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13. ABSTRACT ***(Maximum 200 Words)***

During the 60 months of this project, 23 member institutions of the Cancer and Leukemia Group B (CALGB) and their affiliates entered 347 breast cancer patients into the Linked Registry according to procedures specified in CALGB protocol 9484. Telephone interviews have been completed on 91.4% of eligible patients. Only 8.6% of patients refused the interview. The flow of samples from eligible patients has been satisfactory and there have been no problems with preparation of DNA, or with the handling of serum samples and tissue blocks. Patient accrual was about one tenth of that originally anticipated for this project. Corrective actions taken during the project improved accrual but it never was satisfactory. Changes in the way that the research and ethics communities view large-scale projects in which genomic DNA is collected and studied will be required before projects of this magnitude can succeed. Despite the smaller patient sample resulting from the project, the Registry will be used for selected proposals that meet the its review criteria. At the end of funding arrangements were made to archive the specimens and to preserve the questionnaire-derived data so as to serve investigators who will use the Registry in the future.

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J Ross [signature] October 20, 1999

PI - Signature Date

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Final Progress Report
Contract DAMD 17-94-J- 4114 from U.S. Army Research and Materiel Command

October 1, 1994-September 30, 1999
Prepared by O. Ross McIntrye, M.D. Principal Investigator

INTRODUCTION:

The use of adjuvant chemotherapy following primary breast cancer treatment benefits many patients[1]. On the other hand, adjuvant chemotherapy carries with it a number of potential risks including toxic reactions and secondary malignancies. Thus, it would be desirable to give adjuvant therapy only to the subgroup of women with breast cancer who are most likely to have a recurrence. Although clinical findings are useful in assigning prognosis [2,3], these alone are imperfect measures and there is hope that additional tests, such as the detection of certain somatic mutations in the tumor, will prove helpful in guiding the decision as to who should and who should not receive adjuvant chemotherapy. We have reported that the benefit of high dose adjuvant treatments containing doxorubicin is largely confined to the subgroup of patients whose tumors overexpress erbB-2 or P53[4,5]. We now hypothesize that genes in the germ line also interact with therapy and/or somatic mutations in the tumor to determine the outcome of breast cancer. In order to pursue the testing of this hypothesis large numbers of patients with carefully staged breast cancer assigned to specific treatments will have to be studied. In addition to the usual information on such patients, DNA must be obtained for studies of heritable genes and tumor specimens collected for studies of somatic mutations. Finally, reproductive, family, diet and exposure history information should be gathered on the study population. The purpose of this project is to develop a resource of such patient information and material for investigators who will use it for the purpose of pursuing studies relating to the stated hypothesis. We refer to the resource created by the project as a "Linked Registry", and have developed methods for its use by approved breast cancer investigators.

BODY

In this section of the final progress report the specific technical objectives are listed in the order as approved in the Statement of Work. (Negotiations of the budget with the sponsor resulted in elimination of selected portions of the specific technical objectives as proposed in the original application.)

a. *To modify questionnaires currently in use by CALGB investigators at the University of North Carolina, University of Minnesota and NIEHS to collect key family history and exposure data in a self-completed questionnaire.*

The self completed patient questionnaire contains items from the above sources. The team led by Dr. Fred Li at the Dana Farber Cancer Institute also contributed to the development of the questionnaire. Under the leadership of Dr. Millikan and Ms. Cirrincione a draft self-completed questionnaire was developed that addressed the needs of the patients and was capable of being interfaced with the CALGB Data Management System. Pilot testing in CALGB institutions during the early spring of 1995 revealed several problems that were corrected in a further draft that was tested in April of 1995. The final version of the questionnaire was incorporated in CALGB protocol 9484 that was mailed to CALGB institutions on May 15, 1995 for activation.

In an attempt to improve patient accrual the original protocol was amended in 1996. After approval of the revised protocol by the Army Research and Materiel Command, it contained the following changes:

1. Patients were no longer given the option of receiving the results of familial gene studies performed on their specimens. Such testing had become commercially available thereby obviating ethical issues that had led us to offer to provide test information, if desired by the patient, in the original study design. (See previous progress reports for the background leading to these decisions.) As a result of this change:

- there was no longer a requirement that the institution must have a genetic counseling program in place for the study patients,
- confidentiality issues posed by the return results of research genetic tests to the institution were avoided, and
- since the research results would be located in the CALGB data base at Duke University rather than in the records of about 200 institutions, the process of obtaining a Certificate of Confidentiality from the Department of Health and Human Services would be simplified.

2. Because participants in the amended protocol will not receive information concerning familial gene status, study participants no longer consisted of two groups: those who wish and those who do not wish to know their status with respect to familial cancer genes. Thus portions of the original questionnaire dealing with the topic of the choice to receive information on gene carrier status were no longer relevant. The questionnaire was modified accordingly after pilot testing of these modifications was successful.

The current version of the self completed questionnaire is included in this report as **Appendix 1.**

b. *To establish review procedures and criteria for selecting patients with a family cancer history for further study. Criteria will include, but are not limited to, having one or*

more first-degree relatives with breast cancer or having 2 or more relatives with breast, ovarian, or colon cancer.

The purpose of the self-completed questionnaire was to select patients for a telephone interview. On the basis of information from the self-completed questionnaire, the investigators at UNC, under the direction of Dr. Millikan, categorized the patients into two groups:

1. Patients with any first or second degree relative with breast or ovarian cancer.

2. Patients aged <50 years with no family history

When it became clear that accrual to this project was less than originally anticipated, it became feasible to carry out telephone interviews on all patients instead of only a sample of those without a family history of cancer as originally proposed.

c. *To develop a telephone interview with patients identified for further study that will expand on the screening data collected, obtain information and that will facilitate validation of cancer reported.*

Our previous experience has shown that it is necessary to conduct telephone or in-person interviews to verify and complete family histories and exposure history. Because recall bias is introduced in self-reports of breast cancer occurrence in first degree relatives[6] a carefully administered interview to confirm the self-reporting is indicated. Telephone interviews work as well as in-person interviews for this purpose.[7]

Our in-depth telephone interview was designed to collect information on family history of cancer, reproductive history, occupational exposures, use of hormones, smoking, alcohol, diet, and a variety of other factors. Each of these items had been validated in previous epidemiologic studies conducted by Dr. Fred Li, Dr. Dale Sandler, and Dr. Millikan. In addition, a variety of novel questions relating to onset of menopause related to cancer treatment, use of over-the-counter medications, physical activity before and after cancer treatment, and environmental exposures were collected. The latter items underwent extensive pilot testing and validation prior to inclusion in the telephone interview. Finally, a series of open-ended questions were added at the end of the interview to solicit patients' views on what causes breast cancer, their reaction towards enrollment in research studies, and their opinions regarding the interview process. The telephone interview questionnaire is offered as **Appendix 2.**

A total of 347 patients were enrolled in CALBG 9484 as of September 20, 1999. In-depth telephone interviews were completed on 277 patients. A refusal rate (number of refusals / eligible participants) of 8.6% was obtained. A refusal rate of 10% or less is considered excellent for epidemiologic studies. Table 1

presents a listing of the interview process for the 347 patients enrolled on 9484, as of September 20, 1999.

TABLE 1

Ineligible*	32
Refusal	27
Deceased	5
Too sick**	4
Unlocatable	2
Completed interviews	277
Total	347

*Ineligible: patient was taken off protocol, patient did not speak English, CRA determined patient to be incapable of interview,

**Too sick: patient was not feeling well enough to be interviewed, but agreed to be interviewed at a later date. We intend to follow-up these patients.

Self-administered Family History Forms were obtained on all 277 patients. All 277 telephone interviews have been coded. A total of 200 interviews (four batches of 50 interviews) were data-entered, error checks were run, and the data was transferred to the CALGB Data Management Center (DMC). The final batch of 77 interviews is currently being data-entered. Error checks will be run and the data transferred to the DMC.

d. To collect fixed breast tissue from patients and germ-line DNA, plasma, and urine from the same patients.

1. Development of the protocol covering the collection of specimens and epidemiological data:

CALGB Protocol 9484 specified methods for the collection and shipment of the specimens described above and contained patient consent forms for the study. Our initial experience with this protocol has been reported[8] It defined patient eligibility, limiting participation to those who were entered on a CALGB protocol in which CALGB is responsible for the collection of staging and treatment information (*i.e.* Only non-Intergroup protocols or CALGB patients entered on Intergroup protocols for which CALGB was the coordinating center could be included.). After approval by the Army and by Office for the Protection from Research Risks of the National Institutes of Health, the protocol was activated on June 15, 1995.

To our knowledge, this protocol represents the first prospective multi-institution project in which genomic DNA is collected for studies of cancer related genes on patients who are entered on national clinical trials. We recognized that the studies of germ line DNA with particular reference to familial cancer genes in such a setting could prove problematic. On September 14, 1994 we convened a meeting of experts in the field of

familial cancer gene studies including representatives of the Human Genome Project, members of bodies for review of consent documents for research trials involving humans, and with members of the breast cancer advocacy community to discuss our project. At this workshop we sought advice with respect to the ethical issues involved and offered our draft consent documents for review. The agenda for this meeting and its participants are given in **Appendix 3.** The consent form developed for the protocol was an outgrowth of this meeting.

By year two of the project, it was clear that patient accrual to this study was far less than anticipated and we took steps to address this problem. During year one, it appeared that the availability of genetic counseling within CALGB institutions, a resource needed if the results of testing for familial cancer gene testing were to be made available to study subjects, was the principal stumbling block to adoption of the protocol at many CALGB institutions. (At about this time the results of a survey of NCI supported Cancer Centers revealed that only one-half of them offered genetic counseling[9].) We recognized this need during the design phases of the project and described it in our application.

Beginning in the second year of the project we instituted a CALGB program intended to provide extensive training in genetic counseling skills. Since then, four day-long Genetics Workshops have been held for members of the CALGB. These well-attended meetings have a curricula designed to improve counseling about the risk and benefits to patients who participate in the project.

Despite the progress of the training program, the number of institutions approving the study remained far less than anticipated and it became clear during the second year of support that other aspects of the project also caused concern at many of our CALGB institutions. Our project was conceived and designed to minimize the risks involved in this kind of research, however at this time cautionary articles for the lay and scientific community appeared and generated much publicity.[10] Although these publications recommended that testing for familial cancer genes should occur in the context of research projects, such as is represented by the current study, Institutional Review Boards (IRBs) were not willing to approve testing for familial cancer genes in the context of cooperative clinical trials. We were asked by our investigators to assist in providing information addressing these IRB concerns. Information for submission to institutional IRBs was provided to investigators in a "Question and Answer" format, (**Appendix 4.**)

Additional information concerning the project was provided to all CALGB investigators in the CALGB newsletter during the winter of 1995 (**Appendix 5**). This newsletter article considered the issue of whether a separate new consent (sometimes referred to as a "reconsent" by others) is required for each laboratory test to be performed on samples at some time in the future. The newsletter described the process used to approve and

assign priority for the use of specimens derived from this project. Because there was no further risk to the participant we took the position that further consents were not required but this viewpoint was not shared by some members of the research community.

Further steps were taken in order to improve accrual to the original protocol in 1996. These changes were implemented following approval by the sponsor:

a. Patients were no longer given the option of receiving the results of familial gene studies performed on their specimens. Such testing had become commercially available thereby obviating ethical issues that had led us to offer to provide test information, if desired by the patient, in the original study design. (See previous progress reports for the background leading to these decisions.) As a result of this change:

- there was no longer a requirement that the institution must have a genetic counseling program in place for the study patients,
- confidentiality issues posed by the return of results of research genetic tests to the institution were avoided, and
- since the research results would be located in the CALGB data base at Duke University rather than in the records of about 200 institutions, the process of obtaining a Certificate of Confidentiality from the Department of Health and Human Services would be simplified.

Despite these changes, the number of participating institutions and the number of patients entered into the study increased more slowly than anticipated during the second half of 1996 and the first half of 1997. With the impending closure of CALGB protocol 9344 in July 1997, the major breast cancer adjuvant study led by CALGB and the source of the majority of new CALGB breast cancer patients, the Steering Committee met June 2, 1997 in Chicago to consider further steps that could be taken to improve accrual.

b. Several items that were required by the sponsor in the consent form but that were not relevant to this project were identified as causing problems with local IRB approval. (These are summarized in **Appendix 6.**) Further negotiations led to the removal of these impediments. Fortunately, during this same interval, under the leadership of the Breast Cancer National Action Plan and the National Cancer Institute, a simplified consent document was being drafted. Dr. McIntyre participated in the review of this and, with appropriate editing, the simplified consent document was approved by the Army. It should be noted that language previously required in the consent form and which institutions found troubling has been completely deleted in the revised form. CALGB 9484

with these amendments and revised consent forms is included as **Appendix 7.**

c. A Certificate of Confidentiality covering this project was obtained from the Department of Health and Human Services in 1996. To our knowledge this is the first such Certificate issued to cover the work of a research project in which the research records exist in multiple institutions.

2. Accrual to CALGB Protocol 9484:

Quarterly accrual to CALGB 9484 is shown in Table 2.

TABLE 2
QUARTERLY PATIENT ACCRUAL TO CALGB 9484

Time	Frequency	Percent	Cumulative Frequency	Cumulative Percent
OCT-DEC 95	6	1.7	6	1.7
JAN - MAR 96	9	2.6	15	4.3
APR - JUN 96	17	4.9	32	9.2
JUL - SEP 96	8	2.3	40	11.5
OCT - DEC 96	22	6.3	62	17.9
JAN -MAR 97	41	11.8	103	29.7
APR - JUN 97	31	8.9	134	38.6
JUL - SEP 97	13	3.7	147	42.4
OCT-DEC 97	14	4.0	161	46.4
JAN-MAR 98	37	10.7	198	57.1
APR-JUN 98	30	8.6	228	65.7
JUL-SEP 98	31	8.9	259	74.6
OCT-DEC 98	42	12.1	301	86.7
JAN-MAR 99	35	10.1	336	96.8
APR-JUN 99	6	1.7	342	98.6
JUL-SEP 99	5	1.4	347	100.0

ACCRUAL FOR TREATMENT STUDIES

Time	Frequency	Percent	Cumulative Frequency	Cumulative Percent
OCT-DEC 95	164	7.1	164	7.1
JAN - MAR 96	177	7.6	341	14.7
APR - JUN 96	174	7.5	515	22.2
JUL - SEP 96	161	6.9	676	29.2
OCT - DEC 96	208	9.0	884	38.1
JAN -MAR 97	201	8.7	1085	46.8
APR - JUN 97	116	5.0	1201	51.8
JUL - SEP 97	42	1.8	1243	53.6
OCT-DEC 97	63	2.7	1306	56.3
JAN-MAR 98	156	6.7	1462	63.0
APR-JUN 98	181	7.8	1643	70.8
JUL-SEP 98	194	8.4	1837	79.2
OCT-DEC 98	207	8.9	2044	88.1
JAN-MAR 99	213	9.2	2257	97.3
APR-JUN 99	31	1.3	2288	98.7
JUL-SEP 99	31	1.3	2319	100.0

A total of 347 patients were entered from June 15, 1995, the date the protocol was activated through August 31, 1999, the date that the protocol was closed to new patient entries. The peak quarterly accrual occurred in the period October-December 1998 (42 patients).

During this same time period 2,319 patients were entered on CALGB breast cancer treatment protocols and were potentially eligible for entry onto CALGB 9484 and participation in the Linked Registry. Only 15% of the potentially eligible patients participated. Table 3 shows the quarterly patient entry to CALGB treatment protocols during the period that CALGB 9484 was active.

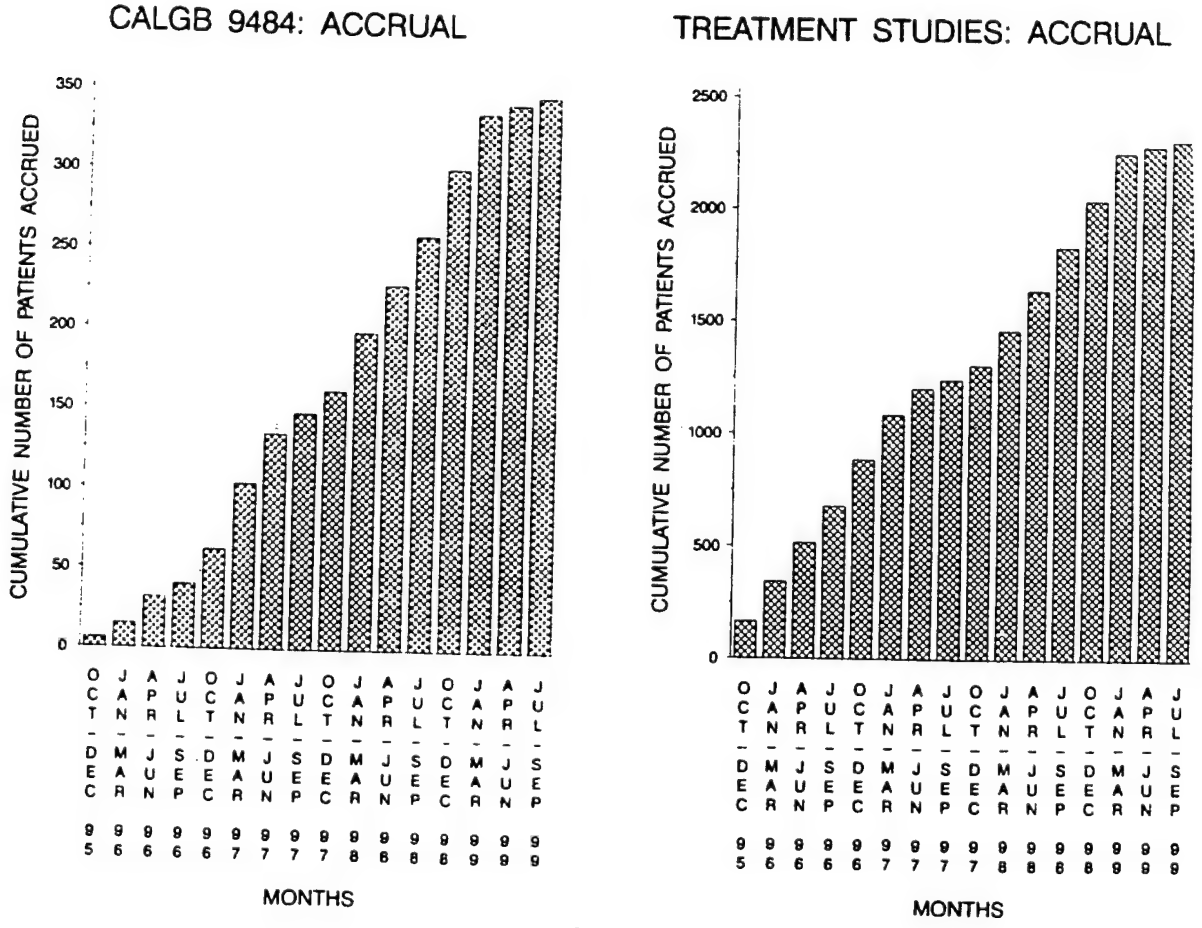
TABLE 3

QUARTERLY PATIENT ENTRY TO CALGB TREATMENT PROTOCOLS

STUDY	Frequency	Percent	Cumulative Frequency	Cumulative Percent
9082	190	8.2	190	8.2
9342	280	12.1	470	20.3
9343	248	10.7	718	31.0
9344	658	28.4	1376	59.3
9741	824	35.5	2200	94.9
9840	119	5.1	2319	100.0

It will be noted that the rate of patient accrual to CALGB 9484 generally followed the accrual rate to treatment studies. Early in the project, however, the fraction of patients entered was relatively smaller. This is shown graphically in figure 1. The various steps taken to improve accrual, described above, may be responsible for the improved fraction of patients that entered later in the project.

FIGURE 1
TREATMENT STUDY AND 9484 ACCRUAL



3. Collection of Specimens:

a. Processing of whole blood for DNA extraction UNC DNA Laboratory

Nearly all patients who have agreed to participate in CALGB 9484 have also agreed to provide a specimen for familial gene studies Since provision of such a specimen is not a requirement for participating in 9484, this indicates that most patients who are informed about the study and agree to participate are willing to have familial gene studies performed.

The UNC Tissue Procurement and Analysis (TPA) Core Facility has received and processed whole blood for DNA extraction for CALGB 9484 since October, 1995. The facility is under the direction of Ms. Lynn G. Dressler who also serves as Vice Chair of the Solid Tumor Correlative Sciences Committee of the CALGB and the coordinator of tissue specimens. The UNC lab is also the approved CALGB DNA extraction facility for breast studies. We have received 336 whole blood samples from 296 unique patients during this time frame (22 patients had multiple blood samples drawn). Most blood specimens received have been obtained prior to treatment. Blood samples collected at the CALGB treating institution are placed inside small plastic transport tubes and shipped to the TPA laboratory by overnight mail at ambient temperature. Samples are accompanied by a CALGB Whole Blood Specimen Routing Form (CALGB Form C-383) which, in addition to other information, indicates the originating institution, CALGB patient identification number, CALGB parent clinical trial, and date of blood draw. Once the specimen is received in the TPA laboratory, the sample is logged into a hardcopy logbook and TPA database and is given a unique laboratory identification number. All DNA vials derived from the sample are identified only with this unique code number. In this way, the TPA facility delinks and anonymizes samples for storage and subsequent distribution to approved investigators. DNA specimens are stored and distributed with a date and code number only. At no time are patient names or CALGB patient numbers associated with the processed DNA sample.

DNA Processing Procedure:
Blood samples are mailed on the day of the blood draw so that all samples can be processed within 48 hours of collection. Briefly, two 10cc tubes of blood from each participant are combined and centrifuged to obtain the packed cell pellet (containing red cells and mononuclear cells). Plasma is removed and the cell pellet is stored overnight at -70°C. The pellet is then thawed at 37°C, the red blood cells are lysed and, following centrifugation, the remaining mononuclear pellet is washed . The resuspended pellet is added to the ABI automated DNA extractor (Applied Biosystems Nucleic Acid Purification System) and precipitated DNA is

captured on a 13mm filter. Following incubation of the filter in a 50°C waterbath extracted DNA is stored at 4°C in microvials.

Estimates of DNA concentration are obtained by optical density readings (OD260/0D280). Following our usual quality control procedures, aliquots of specimens are selected for gel electrophoresis to evaluate quality of the DNA. Of the 336 specimens processed (296 unique patients), 332 (292 unique patients) have been evaluable (good quality DNA; blood received within 48 hours of blood draw) and have yielded a mean total DNA concentration of 437.8 micrograms (range: 14ug-2202ug). Extracted DNA is stored in microvials at 4°C for short term storage. For distribution to approved investigators, DNA will be aliquoted in multiple vials and remaining vials will be stored at -180°C for long term storage. For correlation with clinical outcome, the TPA facility interacts directly with CALGB data management center (DMC) and not with the individual investigator. The TPA facility will provide the CALGB DMC with the unique laboratory code number and date of blood receipt, corresponding to each CALGB 9484 blood specimen received in the lab.

b. Plasma and urine:

Plasma samples are collected into EDTA-containing collection tubes. After separation from the cellular component, the plasma are aliquoted to a freezing tube, labeled, and frozen at -20°C at the participating institution. These samples are batched and, when several tubes have been collected, they are shipped on dry ice overnight. The repository was at the Dana Farber Cancer Institute until 1996 when it moved to Georgetown University (Lombardi Cancer Center) when the director of this part of the project, Dr. Daniel Hayes, moved to that intitution. (Dr. Hayes also serves as Chair of the CALGB Solid Tumor Correlative Sciences Committee and his laboratory is the approved CALGB plasma repository for the Group.

Upon arrival at the repository, samples are catalogued and aliquoted to special freezing tubes and stored at -70°C. The catalogue is maintained in a computerized database (Excel) and has recently been transferred to the CALGB LabTrak system.

Early in the project, difficulties with stability of candidate study molecules in the urine were encountered and urine collection was put on hold. A number of attempts were made to devise a feasible method for procurement, storage, and shipment of urine specimens. Despite these efforts, it was not possible to duplicate the results of in-house specimens with those which were shipped. For this reason, the urine collection portion of the protocol was not activated.

In contrast to the specimens for DNA, plasma specimens were collected on each patient at several clinical milestones (for instance pretreatment, at the end of courses of adjuvant therapy, at relapse, etc.). For this reason the number of plasma samples considerably exceeds the number of DNA

samples. A total of 871 samples from 262 patients have been collected, processed, stored, and catalogued. These are available for study according to the Steering Committee's guidelines.

c. Fixed Tissue:

When the patient signs an informed consent to participate in CALGB 9484 institutional clinical research associates arrange for submission of tissue blocks by contacting the coordinating pathologist at a CALGB main member or affiliate institution. Paraffin blocks and sample submission forms are received at the CALGB Pathology Office (CALGB PCO). During the first four years of the project this office was located at Roswell Park Cancer Institute under direction of Dr. Maurice Barcos. Dr. Carolyn Compton of the Massachusetts General Hospital became the Chair of the CALGB Pathology Committee in 1998 and in April 1999 the Pathology Office moved to Ohio State University. Here, after approval by the Army for the transfer of the subcontract, the procedures originally developed by Dr. Barcos for the project continue with only slight modification under the direction of Drs. Saul M. Suster and Scott D. Jewell. Table 4 presents information concerning the number of tissue blocks and slides received to date from patients on CALGB protocol 9484.

TABLE 4
Tissue blocks and slides received
on CALGB 9484 patients

Study Number	Patients	Blocks	Slides
9484 - only	9	7	7
9092/9484	12	12	0
9342/9484	28	38	12
9343/9484	32	31	31
9344/9484	62	72	2
9741/9484	101	113	0
9840/9484	4	6	0
Totals	248	279	52

Four micron slides are reviewed for accuracy of diagnosis, and areas on the slides containing homogeneous malignant tissue are delineated. At three levels, sections are taken and stained and examined to ensure representative tissues is being distributed for all assays (See Appendices 6 and 7). We ask for permission to retain the blocks for future sectioning and store them at 4° C.

At the time of assay, if the submitting institution requires the return of the tissue blocks, the CALGB PCO cuts and mounts thin and thick sections. At least 30 sections are removed: 20, 4 micron sections for immunohistochemistry/FISH/ISH assays and 10, 10 micron sections for molecular based assays requiring extracted DNA. These procedures incorporate careful quality control and quality assurance parameters, including changing the microtome blade between each block to prevent

contamination of DNA on the blade surface, cleaning the waterbath surface between each block, and wearing gloves to process blocks. As part of the routine processing procedure at the CALGB PCO, sections for H & E staining are cut immediately preceding and after those cut for molecular (10 micron section) and immunohistochemical (4 micron) assays so that three levels are represented for histopathology review. The CALGB Pathology office reviews all H & E sections to ensure that representative and sufficient tumor tissue is present throughout all sections cut for assay. Distribution of samples to approved investigators is defined in CALGB 9484 (see Steering Committee oversight) and is rigorously monitored both in-house and through the CALGB DMC Lab Trak system.

e. *To review and confirm the histopathological diagnosis of breast cancer on submitted tissue*

The review to confirm the diagnosis was originally conducted by Dr. Barcos and colleagues. With the move of the Pathology office to Ohio State University, this review is now conducted by Dr. Saul Suster and his staff.

The Pathology Coordinating Office has developed an integrated coordination and communication system responsible for the collection, archiving, surveillance, quality control and quality assurance of the fixed, paraffin tissue blocks for this study. The appointment of Lynn Dressler as the Coordinator for solid tumor correlative science studies as well as the Vice Chair of the Solid Tumor Correlative Sciences Committee of the CALGB expedites this integration. She interfaces with database management, maintaining appropriate quality control and quality assurance procedures for the storage and processing of tissues, and developing policies in response to tissue banking concerns by institutional pathologists. In addition, we have identified coordinating/contact pathologists at each of our main and affiliate institutions to expedite case accessioning of paraffin blocks and have established a network of communication for responding to problems that may develop during the course of the study.

In 1997, Dr. Ira Bleiwess of Mount Sinai Hospital was named as the coordinating pathologist for CALGB breast cancer studies and was named to the Steering Committee for the project. Pathology Workshops are held at CALGB meetings to disseminate information regarding the Linked Registry project and to discuss the active role that pathologists can play in this study. In addition the workshops provide a forum for problem resolution with respect to accession and tissue banking.

A more detailed description of the quality control and quality assurance methods used in this part of the project is included as **Appendix 8.** It will be noted that when an Intergroup Specimen Banking Committee met to consider methods for the handling of tissue specimens, most of the procedures adopted was derived from the experience of CALGB with this project (**Appendix 9**).

f. To integrate information about specimen receipt, specimen availability, and laboratory testing results with the CALGB data base and to prioritize use of this information.

1. Data Management:

Tracking System: Under the leadership of the CALGB Group Statistician, Stephen George and the day to day supervision of Michael Moloney at the CALGB Data Management Center, a system for tracking specimen receipt and specimen availability was developed. Referred to as Lab Trak , this system addresses the problem of identifying multiple samples on large numbers of patients and knowing the status of the specimen at various points in the history of that specimen. A more complete description of this system is included as **Appendix 10.**

Integration of information from this project: Under the leadership of Ms. Donna Hollis and Gloria Broadwater at the CALGB Statistical Center methods for entry of the information from the epidemiological questionnaire into the CALGB database system have been developed. As results of laboratory studies performed by users of the registry are gathered the second portion of this task will be performed, namely the integration of this information with clinical characteristics, response to treatment and other endpoints.

As anticipated, there is a lag in the incorporation of data from this project into the database, so that the database does not currently reflect the work that has been accomplished. For instance, the data base at the Data Management Center currently has reports on DNA samples from 135 registered patients while the DNA laboratory at UNC has received specimens for DNA from 296 patients. Good quality DNA has been prepared from samples on 292 of the 296 patients. Likewise the Data Management Center has recorded information on tissue blocks from 145 patients, while we expect eventually to receive and enter tissue block information on about 80% of the 347 patients on CALGB, or about 277 patients. This delay is occasioned by careful review and error checking before information enters the database at the Data Management Center. As this progress report was prepared, the Data Management Center records only 71 patients with information about both DNA and tissue blocks. During the next several months, the information at the Data Management Center will come into line with that currently available in the laboratories.

Investigators will be furnished with coded specimens from the project and return the results of laboratory testing to the Data Management Center where these results will be entered in the database. Under the direction of CALGB statisticians the analyses requested by the laboratory investigators will be carried out. With this approach laboratory investigators remain "blinded" with respect to clinical characteristics and outcomes of patients whose samples they have studied until after they have reported their results.

2. Prioritization of Use:

Previous progress reports have documented proposals for the use of the Linked Registry Resource by a number of investigators both from within and without the membership of the CALGB. In each case, the small number of patients in the Registry has prevented its use for the type of study proposed by these investigators. For this reason, the Steering Committee has elected to postpone use of the Registry until after October 1, 1999 when accrual is completed and most of the patient materials received. During its November 1999 meeting, the Steering Committee will examine two proposals for use of the Registry, one from within the CALGB membership and another representing a collaboration of a CALGB member with an investigator from the Human Genome Project at the Lawrence Livermore National Laboratory.

Written proposals from the scientific community are considered by the Steering Committee if they do not compete with approved projects already underway, and are prioritized with respect to anticipated amount of tissue or resources consumed vs. the likely yield of important information. In assigning this priority to scientists who are not CALGB members we use the same scale that will be used for projects developed by CALGB members. In all cases emphasis is placed upon the level of innovation and the track-record of the investigator with respect to peer review and publications. We plan to deliberately include projects, however, from young investigators without a track record, if they are endorsed by knowledgeable mentors, are innovative and appropriately use these valuable specimens.

All proposed uses of the Linked Registry must be described in formal protocols that define the objectives, methodology, and statistical assumptions. These are subjected to peer review by individuals chosen by Dr. Daniel Hayes, the Chair of the CALGB Solid Tumor Correlative Sciences Committee. Reports of this review are then considered by the Steering Committee which then evaluates the proposal and assigns priority to it.

Investigators using the Linked Registry receive a letter outlining the nature of their collaboration with the Registry. The investigators must confirm that they agree to the terms of the collaborative agreement before specimens are shipped to them. A copy of the letter of agreement is furnished as **Appendix 11.**

The availability of the Linked Registry is publicized through usual channels of scientific communication including publications and scientific meetings. During the fourth year of the project, the difficulties in achieving the anticipated accrual were the subject of a poster presentation at the *Era of Hope* meeting sponsored by the Army Breast Cancer Research Program. In addition, the CALGB newsletter that is sent to many investigators outside the CALGB has been used to describe the creation of this resource. Information about CALGB 9484 is available on CALGB's website.

g. *To augment resources at CALGB institutions in order to procure the above described information and specimens.*

Institutions have received a payment of $275 for each patient entered on CALGB 9484. This is used to defray the costs of locating, documenting, reviewing and preparing tissue blocks and drawing blood specimens for shipment. Costs of shipment have been billed to the Central Office account supporting the project. The budget available for this project does not allow a payment that covers the full costs to the institution for participating in the trial but the payment assists the institution in its participation.

Relevance to the original hypothesis:

The resource that has been created is clearly of insufficient size to test portions of the original hypothesis. During the design phase of the project, we projected that a successful project would yield a Registry containing information on up to 3,000 patients. In fact, during the project period, the CALGB had access to 2319 patients who were potentially eligible for participation in the registry. Using several estimates for the frequency of familial cancer genes in a group of this size we estimated that 30 to 90 of these patients might be found to have a familial cancer gene as revealed by study of their DNA. Given the various stages of disease represented by the subpopulation with familial cancer genes and the different adjuvant schedules assigned to them, it may be seen that our originally proposed study population was marginal with respect to the types of hypotheses that could be tested.

When it became clear that efforts to increase the fraction of breast cancer patients who participated in this project were of marginal success, those involved considered several options. The first of these was to pursue changes to the protocol that would increase accrual. These could provide information about how to design a future project that might achieve the success originally hoped for in this project. Our recommendations on this topic appear in the Conclusions section, below.

Secondly, the Steering Committee has altered its strategy and is considering requests for the use of the Registry that fall into the pilot project category, rather than studies that will attempt to draw major conclusions about the genome and breast cancer treatment outcome. As the Registry database is completed over the next few months, the Steering Committee expects to approve several such collaborations. As originally designed, the last year of the project was to be devoted to completing the database. Because of our desire to register as many patients as possible, patient accrual continued into an extra (fifth) year of the project (without additional funds), and the resources required to complete the database will come from within the CALGB.

Finally, it is necessary to comment upon the strength of the original hypothesis. There are certainly those who feel that a search for a relationship between the genome and cancer outcome unlikely to be fruitful because of the myriad possible confounding genetic interactions. However, despite the commercial availability of laboratory tests for familial cancer genes for over four years, the relationship

between the presence or absence of one of the known familial breast cancer genes and treatment outcome, if any, is not yet known. This is a relatively simple question to answer once information is collected about familial gene status on an adequately sized group of carefully staged patients receiving defined therapy. If our project had been entirely successful we would have had an answer to this question.

It is also worth commenting upon the relationship between somatic alterations in cancer and treatment outcome. Early in the history of work in this area there were those who felt that the issue was so complex that efforts to explore the area were impractical. Recent history, we believe, has shown that this pessimistic view is not warranted. The observations concerning the relationship between erbB-2 and treatment outcome that CALGB reported been confirmed by others[11]. Other evidence, from studies in leukemia, establishes a link between somatic mutations and treatment outcome. For instance the t(15;17) translocation found in acute promyelocytic leukemia generates a chimeric protein that is targeted by all-trans-retinoic acid[12]. Only the extreme optimists who were involved in the early cytogenetic studies in leukemia would have predicted that such a specific relationship between chromosome abnormalities and treatment outcome would be found.

Recommended changes in future projects of this type are presented in the Conclusions Section of this report. We feel that it is essential for a successor project to develop a registry covering the large number of patients required to address our hypotheses and we anticipate developing such a proposal.

KEY RESEARCH ACCOMPLISHMENTS

- We have created what is to our knowledge the first repository of germline DNA from protocol-treated breast cancer patients participating in multi-institutional clinical trials and have linked this resource with comprehensive clinical information. Coupled to this resource is data derived from an extensive epidemiological questionnaire. Tissue specimens and multiple plasma samples from these patients complete the repository. In summary we:

  a. developed and validated epidemiological questionnaires (self completed and telephone administered) for patients with breast cancer,

  b. collected tissue blocks, peripheral blood for DNA, serum, and epidemiological data on 347 breast cancer patients entered on the treatment protocols of the CALGB,

  c. established reference laboratories and prepared samples for storage and distribution to qualified breast cancer investigators, and

  d. developed and implemented a method for tracking specimens.

- We discovered the many impediments to creating a resource such as this. There were problems arising from an attempt to integrate studies of familial cancer genes

into large scale clinical trials. Many of these problems were corrected during the period of support.

- This project provides the groundwork necessary for the design of a larger national repository of breast cancer genetic material and information. Recommendations for future national studies of this type have been developed and are presented elsewhere in this report.

- Several investigators who will use the resources created by this project have been identified. It is anticipated that others will be approved for use of the registry in the near future.

- Four full-day Genetics Workshops have trained more than two hundred physicians, nurses, and clinical research associates in aspects of human genetics relating to breast cancer and the conduct of this project.

REPORTABLE OUTCOMES

Manuscripts:

(Note: apart from the experimental design issues dealt with in the one manuscript reported, most papers using the Registry will be based upon use of the Registry by investigators who will perform their work with specimens and epidemiological data obtained from it. Thus the bulk of the publications from this project are yet to come.)

Millikan RC, Kornblith AB, McIntyre, OR, Berry DA, Broadwater GJ, Sandler DP, Karas K, Dressler L, Gross LS, Collyar DE, Schilsky RL. Genetic testing in breast cancer cooperative clinical trials, barriers and opportunities. Cancer Therapeutics 1:95-99, 1998 **(See appendix 12)**

Poster presentations:

BREAST CANCER GENETIC STUDIES INCOOPERATIVE CLINICAL CANCER TRIALS
O. R. McIntyre, MD, R. C. Millikan DVM, MPH, PhD, L. Dressler, MA, A. B. Kornblith, PhD, D Berry, PhD, Maurice Barcos, MD, D. Sandler,PhD, D. E. Collyar, BS (Presented at the "Era of Hope Meeting, Washington, DC. October 31, 1997) See Appendix 14 for the text of this poster.

Development of repositories:

The primary purpose of this award was to create a shared resource – a repository of epidemiological data and specimens for use by multiple investigators. The details of this activity are given in the body of this report. The repository created by this project has collected far more comprehensive information from the patients with breast cancer who donated specimens than standard repositories. Detailed information concerning the staging, treatment and outcome of breast cancer is available on each of the patients. In addition, the epidemiological questionnaire

provides extensive data concerning reproductive, dietary, exposure, and family history on these patients. The repository also has successfully collected breast cancer tissue and plasma on the patients. Finally and most importantly we were able to collect blood for germ line DNA on most of the patients who participated in the project. Collectively these activities have created a unique resource for pursuit of attractive hypotheses concerning the causes and treatment/prevention of breast cancer. For more information on the repository see the Body of this report.

Informatics:

A system of identifying, coding, and tracking specimens from the nearly 100 institutions participating in the project was developed, pilot tested and implemented. This information system represents the first comprehensive specimen tracking system within the Cancer Coopereative Groups and was made possible by funding from this project. It represents the prototype of systems that will be required for all such studies in the future. For instance, it was used as the prototype system by the Intergroup Specimen Banking Committee. The Lab Trak system developed by the project is described in **Appendix 10.**

Training:

Four annual full-day Genetics Workshops trained over 200 physicians, nurses, and clinical research associates in aspects of human genetics relating to familial breast cancer genes. In addition five graduate students at the University of North Carolina, Chapel Hill, received training during their participation in developing the telephone interview instrument and family history form. They participated in pilot testing the questionnaire and in other aspects of the project at that institution.

LIST OF PERSONNEL RECEIVING PAY FROM THIS RESEARCH PROJECT:

AT DARTMOUTH, October 1,1994 to September 30,1999

O. Ross McIntyre, M.D, Principal Investigator

AT DARTMOUTH, October 1, 1994-April 1, 1995
Priscilla Stoner,
Karen Sartell,
Mary Sherrell,
Maureen Wetmore,

AT UNIVERSITY OF CHICAGO, April 1, 1995-September 30,1999

Michael Kelly,
Kathy Karas,
Karen Sartell,
Rena Cristwell,
Mary Sherrell,
Deborah Bryant,
Janice Haddon,
Robert Blount-Lyon

AT DUKE UNIVERSITY

Donald A. Berry
Connie Cirrincione
Deborah E. Sawyer
Sandra Bothun
Teryl H. Harris
David Mitchell
Michael Moloney
Joann Burnette
Robert Rose
Joann Wearing

AT UNIVERSITY OF NORTH CAROLINA

Carol Dunmore
Georgette Regan
Pat Plummer
Diane Mattingly
Theresa Nalevaiko.
Jessica Tse
Joanna Smith
Daynise Skeen
Qing Yang
Lynn Johnson
Yan Jin
Mika Bessho
Carol Morton
Diana Lackey
Denise Coon
Bob Millikan
Lynn Dressler
Edison Liu

AT GEORGETOWN UNIVERSITY

Solomon Kebede

AT DANA FARBER CANCER INSTITUTE

Andrew Ackerman

AT THE OHIO STATE UNIVERSITY MEDICAL CENTER

Saul Suster
Scott Jewell
Cindy Coleman
Mary Marin
Tina McKeegan

AT ROSWELL PARK CANCER INSTITUTE

Wayne Stanfield
Joan Natiella

Elaine Bauer
Diane L. Litzinger
Grace A. Kuwik

CONCLUSIONS AND RECOMMENDATIONS

Despite the endorsement of this project by experts in the field of human genetics, breast cancer patient advocates, and leaders of cancer clinical trials in breast cancer we found substantial obstacles in our pathway to create the unique resource represented by this project. We were successful in enrolling 15% (347) of otherwise eligible patients in this project. We collected epidemiological data, plasma, tissue specimens, and germ line DNA, developed the first comprehensive specimen tracking system linking the 100 participating medical centers, and pioneered difficult resolutions to human consent issues. The resource created by our project will be useful for future pilot studies. It will not, however, be able to answer pressing questions bearing on the hypothesis originally proposed, namely, that germ line genes affect tumor progression, interact with somatic mutations, and possibly, influence response to treatment. This experience provides the groundwork necessary for the design and conduct of a much larger project. Despite the hardships encountered by this initial foray into large-scale studies of germ line genes and cancer outcome, the creation of a resource that will enable various tests of the general hypothesis is an important goal that should not be abandoned. Perhaps this understanding is the most important product of our efforts.

In the sections below we first describe the major lessons from the project and then offer our recommendations for generating a project that will recruit a sufficient number of breast cancer patients to answer the important genetic hypotheses that deserve testing.

What are the major lessons from this project?

- The enthusiasm for this project manifested by the investigators and by the scientific review process was not matched by individuals who were responsible for approving and implementing the project at the local level. Many of them lacked an understanding of the structure and function of NCI supported Clinical Cooperative Groups and the safeguards for participants incorporated into this type of clinical investigation. They were also influenced by media reports concerning the risk of liability inherent in performing tests for familial cancer genes. Notwithstanding the recommendation in scientific articles at the time that studies of familial cancer genes should go forward in the context of studies such as the current project, they often failed to endorse local participation in the project. At the conclusion of the project less than half of the 200 CALGB institutional Investigational Review Boards (IRBs) had approved the project.

- Coordinating the activation of the protocol covering the project (CALGB 9484) with the activation of the major breast cancer adjuvant treatment study being conducted by the Group proved to be impossible. Both protocols had to be reviewed by the more than 200 CALGB institutional IRBs – a slow process in which the protocols were usually not linked during the review. Although IRBs have achieved a reasonable "comfort level" as they review treatment

protocols, this did not extend to a protocol where material for familial cancer genes was being collected.

- If all IRBs had approved the project, the number of patients entering the protocol might have doubled. This would have increased the fraction of patients who participated from 15% to 30% of those eligible. An entirely successful study should recruit 90% or more of those patients who enter the treatment trial. Because the protocol covering the treatment trial and the protocol covering this project were separate, and separate consent documents were used for each, the "red tape" required to enter a patient into this project was approximately doubled. Investigators complained about the time and effort required to secure an informed consent for the familial gene study and the "red tape" cost inherent in sample procurement, sample documentation and shipping. Although some of these costs were reimbursed by the project, this payment was an insufficient inducement to participation.

- Although we were ultimately able to secure a Certificate of Confidentiality from the Department of Health and Human Services (HSS) covering the results of this study, this approval came through late in the second year of funding. Because the patients were to be potentially derived from about 200 institutions, it appeared initially to HSS that it might be necessary for 200 such certificates to be issued.

- Delays in approval of the project at the local level allowed the major adjuvant trial from which eligible patients could have been drawn to progress without the opportunity to enroll patients. When this high accruing trial was completed, CALGB entered such patients on a new Intergroup trial managed by another Cooperative Group. Confusion about patient eligibility for CALGB 9484 on this new trial arose.

- When the Registry project was interfaced with a Cooperative Group treatment trial it brought the policies of the two different entities funding these two separate projects into juxtaposition. Once this occurred significant differences in the written policies of the two funding agencies concerning protection of human subjects were noted when it was elected to amend or change our consent forms for the trial. Until this impasse was removed, it was not possible to have a single consent form covering participation in both the Registry and the treatment trial. The result was a doubling of the "red tape" at the institutional level.

- Missing from the milieu in which the Registry was mounted was a public relations effort to make the community aware of the benefits that could flow from the project. In fact, during the first years of the project the media broadcast sharp warnings concerning the risk to individuals that could result from such projects. As there are still some today in the scientific community who question the wisdom of the Human Genome Project, there are those who feel that the hypothesis on which our project was based is not worth testing. Fortunately, this perspective seems to be changing.

How can we make use of the lessons we have learned?

- This project was approved because those in the research community who are advocates of this approach believed, as did those who proposed the project, that our communities were ready to accept a test of these important hypotheses. The fact that a smaller number of patients were registered to the project than originally planned, does not necessarily indicate that the community does not accept the goal of testing the several hypotheses. The breast cancer patient advocacy community certainly endorsed and supported the project and was extremely helpful during our efforts to generate effective processes leading to patient consent and participation. In retrospect, some of the problems that the project encountered could have been revealed by a limited study in which feasibility was the major endpoint. On the other hand, a study limited to several institutions would not necessarily reveal the scope of problems encountered when the project was expanded to the number of institutions required in order to generate the large number of patients required to test the hypotheses. Thus our project proved to be a multi institution feasibility study. We conclude that the processes we used are feasible and when the lessons we have learned are applied, a study on a much larger scale is feasible.

- A long lead-time, about two years, is required to launch a successful study. During this time a Certificate of Confidentiality should be obtained from HHS prior protocol activation. The study should start simultaneously with a new large, probably Intergroup cooperative clinical trial testing breast cancer adjuvant therapy. Depending upon the projected accrual of the treatment study it might need to continue through a second treatment trial. The study should be based upon statistical design considerations considered at the time, but should not go forward unless recruitment of 3,000 to 5,000 patients was planned.

- Responsibility for IRB approval of the study should be based within a single body. The recent decision of the NCI to perform a pilot test of a "national" IRB for certain clinical trials represents a step that could make this precondition feasible.

- If one agency funds the clinical trial and another the Registry, the funding agencies should delegate responsibility for human subject review and approval of the two trials to a single IRB. The two year lead time, mentioned above, should be used to educate this IRB with respect to the procedures employed by the study to safeguard confidential information and to protect the identity of study subjects.

- A single consent document for the two studies should be used. Whereas having a separate signed consent for participation in a study in which familial cancer genes are studied is now standard, there is no need to have this consent in a separate paper document. The goal here is to diminish the "red tape" at the participating institution by having only one document rather than two.

- Funding agencies should adopt a common stance with respect to the liability for patient care as a result of the conduct of genetic studies. The language suggested by the Office for Protection from Research Risks (OPRR) in consent forms is widely accepted and should be used.

- The study design should not require "reconsent" of the patient for each specific research test that will be performed on the patient's sample. The scientific questions that might be asked in future years cannot be stated at the time of sample procurement. Nevertheless, whatever laboratory studies are perfomed on the patient derived samples in the future, they pose no additional risk to those already described in the consent form. The patient can be informed as to the general nature of such tests and the process by which decisions will be reached in order for any specific future test to be done on the sample. If reconsent for each and every future laboratory test, with all the effort that entails at the local level, is thought to be necessary, then the project is not economically or managerially feasible.

- The study design should not include providing information derived from research laboratory tests (tests that have not yet met regulatory approval) to the patient.

- The standards for specimen procurement, distribution, quality assurance by members of the Linked Registry Steering Committee and which form the basis for the approved practices for specimen handling within NCI supported cooperative clinical trials have proved satisfactory. These standards should be incorporated as a part of any future registry project.

- The Lab Trak system or a modification of it should be used to label, code, and track specimens obtained during the project.

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APPENDIX 1. FAMILY HISTORY OF CANCER QUESTIONNAIRE (SELF COMPLETED)

FAMILY HISTORY OF CANCER QUESTIONNAIRE
INSTRUCTIONS FOR CALGB PERSONNEL

A. Purpose - The enclosed survey is part of a recently funded project entitled, "Linkage of Molecular and Epidemiologic Breast Cancer Investigations: A Specialized Registry."

We will be using family history information to select patients for participation in a Registry. The Registry will undertake a systematic collection of tumor specimens, as well as treatment outcome, epidemiologic, and molecular data from breast cancer patients enrolled in clinical trials sponsored by CALGB. Several research hypotheses will be investigated using the Registry, including the role of family history in breast cancer prognosis.

B. Form Specific Instructions

1. Please provide this survey to all patients participating in Protocols _____.

2. We request that the patient complete this questionnaire at the time of treatment with a *RED FELT TIP PEN*.

3. After the questionnaire is complete, return it to the data management representative at your institution.

4. The questionnaires will then be mailed to the CALGB Data Management Center at the following address:

CALGB Data Management Center
2200 West Main Street, Suite 340
Durham, North Carolina 27705

5. Please try to ensure that all patients on the Protocol are given this questionnaire.

If the patient cannot complete the questionnaire at the time of treatment, they may take it home, but should bring the questionnaire with them at the next treatment.

FAMILY HISTORY OF CANCER QUESTIONNAIRE

Instructions for Patient

Thank you for taking time to complete this confidential questionnaire.

We will ask you about the occurrence of breast and other cancer in your relatives. All of the information you provide on this questionnaire will be held in the strictest of confidence. Neither your name nor any identifying information will appear in any report of the survey.

Based upon your answers to the family history questions, we may wish to contact you again for further information. There is a place on the questionnaire for you to tell us how to reach you in the future. With your help, we hope to learn more about the causes of breast cancer.

At the end of the questionnaire on pages 10 and 11 are comment pages. Use these pages if you need to more fully explain any of your answers. You will also find a space to describe special feelings or insights that you may have about the causes of breast cancer.

If you have any questions about our study or the questionnaire, please feel free to call us toll free at:

1-800-xxx-xxxx Monday - Friday 9 a.m. - 5 p.m.

If a representative is not immediately available, you may leave a message and we will return your call as soon as possible.

When you finish the questionnaire, place it in the envelope provided, and return it to the nurse when she returns to your room.

Thank you very much for your participation.

FAMILY HISTORY OF CANCER QUESTIONNAIRE

INSTRUCTIONS FOR COMPLETING THIS SURVEY

Please proceed with the remainder of the questionnaire. We will be asking questions which require you to provide information about history of cancer in your close relatives.

Make an "X" through the circle which represents your chosen responses with a *RED FELT TIP PEN.*

Example:

Please answer all questions to the best of your ability.

IMPORTANT:

We are asking you about the occurrence of cancer in your full-blood relatives.

We are not referring to step-children, step-siblings, or other half-relations.

If you are adopted and are not able to provide information on blood relatives, please skip to comment pages 10 and 11 at the end of the questionnaire.

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form	C-377
CALGB Study No.	
CALGB Patient ID.	

Patient's Name _____ Participating Group _____

Patient Hospital Number _____ Participating Group Protocol No. _____

Main Member Institution/Adjunct _____ Participating Group Patient No. _____

Today's Date

What is your main language: E-English, S-Spanish, O-Other:

(E) (S) (O)

Do you have a phone? N-No, Y-Yes

(N) (Y)

Can we contact you again? N-No, Y-Yes

(N) (Y)

Can we contact you by phone or mail? N-No, Y-Yes

(N) (Y)

Please give us the names, addresses, and phone numbers of two people who will know where you are at all times

Name _____

Address _____

_____

Telephone Number: ( ) _____

Name _____

Address: _____

_____

Telephone Number: ( ) _____

What is your present marital status? N- Never Married, M-Married, W-Widowed, S-Separated, D-Divorced

(N) (M) (W) (S) (D)

Are you adopted? Y-Yes, N-No, D-Don't know

(N) (Y) (D)

If "Yes," please read the following:

If you are adopted and you DO NOT KNOW about the cancer history of your blood relatives, please skip to comment pages 10 and 11 at the end of the questionnaire.

We are asking about history of cancer in your blood relatives.

Do you have any full sisters?

(N) (Y) If yes, please specify how many _____

Do you have any full brothers?

(N) (Y) If yes, please specify how many _____

Do you have any daughters?

(N) (Y) If yes, please specify how many _____

Do you have any sons?

(N) (Y) If yes, please specify how many _____

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form: C-377
CALGB Study No.: _____
CALGB Patient ID.: _____

	Relative	Is Relative Alive, Dead or Unknown	Current Age or Age at Death						Has this Relative ever had a diagnosis of cancer? No, Yes, or Unknown	Types of Cancer (fill more than one circle if necessary)				If other specify type of cancer
			Under 20	20 - 39	40 - 49	50 - 59	60 - 69	70 or over		Breast	Ovarian	Colon	Other	
	Example	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(4)	*Stomach*
1	Mother	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
2	Father	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
3	Sister1	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
4	Sister2	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
5	Sister3	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
6	Sister4	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
7	Sister5	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
8	Sister6	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
9	Sister7	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
10	Sister8	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
11	Sister9	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
12	Sister10	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
13	Brother1	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	
14	Brother2	(A) (D) (U)	(1)	(2)	(3)	(4)	(5)	(6)	(N) (Y) (U)	(2)	(2)	(2)	(2)	

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form: C-377
CALGB Study No.: _____
CALGB Patient ID.: _____

	Relative	Is Relative Alive, Dead or Unknown	Current Age or Age at Death						Has this Relative ever had a diagnosis of cancer? No, Yes, or Unknown	Types of Cancer (fill more than one circle if necessary)				If other specify type of cancer
			Under 20	20 - 39	40 - 49	50 - 59	60 - 69	70 or over		Breast	Ovarian	Colon	Other	
15	Brother3	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
16	Brother4	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
17	Brother5	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
18	Brother6	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
19	Brother7	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
20	Brother8	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
21	Brother9	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
22	Brother10	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
23	Daughter1	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
24	Daughter2	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
25	Daughter3	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
26	Daughter4	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
27	Daughter5	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
28	Daughter6	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
29	Daughter7	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form: C-3
CALGB Study No.: _____
CALGB Patient ID.: _____

	Relative	Is Relative Alive, Dead or Unknown	Current Age or Age at Death						Has this Relative ever had a diagnosis of cancer? No, Yes, or Unknown	Types of Cancer (fill more than one circle if necessary)				If other specify type of cancer
			Under 20	20 - 39	40 -49	50 - 59	60 -69	70 or over		Breast	Ovarian	Colon	Other	
30	Daughter8	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
31	Daughter9	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
32	Daughter10	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
33	Son1	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
34	Son2	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
35	Son3	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
36	Son4	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
37	Son5	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
38	Son6	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
39	Son7	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
40	Son8	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
41	Son9	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	
42	Son10	A D U	1	2	3	4	5	6	N Y U	2	2	2	2	

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-377
CALGB Study No.:	
CALGB Patient ID.:	

EXTENDED FAMILY

Do you have any other relatives who have been diagnosed with cancer? N-No,Y-Yes

(N) (Y)

If yes please complete the table below:

Relative	Alive or Dead	Type of Cancer
Example: Grandmother	Alive	Ovarian

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

FAMILY HISTORY QUESTIONNAIRE
COMMENT PAGE

THANK YOU FOR COMPLETING THE FORMAL PART OF OUR QUESTIONNAIRE. BASED UPON YOUR ANSWERS TO THES QUESTIONS, WE MAY CONTACT YOU IN THE FUTURE. YOU MAY BE ASKED TO PARTICIPATE IN FUTURE STUDIES WHIC ARE AIMED AT INCREASING OUR UNDERSTANDING OF BREAST CANCER. YOUR CONTRIBUTIONS TO THE ON-GOING EFFOR TO UNDERSTAND AND PREVENT BREAST CANCER ARE INVALUABLE TO US.

Please feel free to provide explanations for your answers to any of the preceding questions.

CALGB: FAMILY HISTORY OF CANCER QUESTIONNAIRE

CALGB Form:	C-377
CALGB Study No.:	_____
CALGB Patient ID.:	_____

COMMENT PAGE

Please use this page to write down any special feelings or insights that you may have about breast cancer. We are interested i what you think may have caused your breast cancer.

APPENDIX 2. CALGB FAMILY HISTORY AND EXPOSURE TELEPHONE INTERVIEW

Interviewer ID: _____
Time Interview Began: _____ am/pm
Time Interview Ended: _____ am/pm
Date of Interview: _____
Outcome Code: _____
Reference Date: _____

CALGB DETAILED FAMILY HISTORY AND EPIDEMIOLOGY TELEPHONE INTERVIEW

Hello, my name is _____. May I please speak with (RESPONDENT)? I'm calling from THE LINEBERGER CANCER RESEARCH CENTER AT THE UNIVERSITY OF NORTH CAROLINA CHAPEL HILL. WE ARE CONDUCTING A STUDY ON BEHALF OF CANCER AND LEUKEMIA GROUP B (CALGB).

A. Recently, you indicated your willingness to participate in a study we are conducting of breast cancer patients.
As you recall, we are conducting phone interviews as part of this study. We would like to ask you some questions about your health history. These questions will take about one hour to answer.
Is this a convenient time for you?

(If NO, reschedule.)

If YES:

Thank you very much. Your answers to these questions will help us to understand more about breast cancer. For your future reference here is my name and address:
Name:_____
Lineberger Comprehensive Cancer Center, University of North Carolina
CB# 7500, Chapel Hill, NC 27599
Phone: 1-800-449-0147

B. Your cooperation in the survey is entirely voluntary, and all the information collected will be confidential. Neither your name nor any other identifying information will appear in any report of the survey.

C. The interview will take about 60 minutes. First, I would like to verify some of the previous information you have provided to us.

GO TO SECTION A.

A. VERIFICATION OF PREVIOUS INFORMATION

I. DEMOGRAPHIC INFORMATION

A1. What is your birthdate? _____mm _____dd _____yyyy

A2. What is the highest degree or year of school you have completed? (DO NOT READ CATEGORIES)

[ ] LESS THAN 8 YEARS
[ ] 8 THROUGH 11 YEARS
[ ] 12 YEARS OR COMPLETED HIGH SCHOOL
[ ] SOME COLLEGE
[ ] COLLEGE GRADUATE
[ ] MASTERS
[ ] DOCTOR OR LAWYER (PH.D., M.D., J.D.,D.V.M.)
[ ] OTHER (SPECIFY: _____)

A3. Would you describe yourself as white, black, Hispanic, Asian, or other? (IF OTHER, PROBE FOR ETHNIC GROUP OR RACE)

[ ] WHITE
[ ] BLACK
[ ] HISPANIC OR MEXICAN AMERICAN
[ ] ASIAN OR PACIFIC ISLANDER
[ ] NATIVE AMERICAN
[ ] ALASKAN NATIVE
[ ] OTHER (SPECIFY: _____)

A4 What is your present marital status?

☐ Single
☐ Married
☐ Separated
☐ Divorced
☐ Widowed

A5. IF EVER MARRIED: What is the highest degree or year of school that your husband or partner completed? (DO NOT READ CATEGORIES; IF MORE THAN ONE HUSBAND/PARTNER, ASK FOR MOST RECENT)

[ ] LESS THAN 8 YEARS
[ ] 8 THROUGH 11 YEARS
[ ] 12 YEARS OR COMPLETED HIGH SCHOOL
[ ] SOME COLLEGE
[ ] COLLEGE GRADUATE
[ ] MASTERS
[ ] DOCTOR OR LAWYER (Ph.D., M.D., J.D.,D.V.M.)
[ ] OTHER (SPECIFY: _____)

A6. In what kind of community do you currently live?

Location	Living now in:
Large city (pop.>100,000)	
Suburb of large city	
Town or city (pop.50,000-100,000)	
Town (pop.<10,000)	
Rural, non-farm (in the country, but not a farm)	
On a farm	

II. FAMILY HISTORY OF CANCER

Now, I would like to review the information that you previously provided to us on the Self-Aministered Family History of Cancer Questionnaire.

First I would like to verify that we are asking about your **FULL BLOOD** Relatives.

A7. **Are you adopted?**

☐ **YES, if yes do you know the health status of your full blood relatives?**
☐Yes, then continue with Family History section. ☐ No, skip to B section and continue questions.

☐ **NO,not adopted, continue with Family History section.**

A8. Now I will be asking about all your full blood relatives and how many you have.

HOW MANY?

RELATIVES	NUMBER
SONS	
DAUGHTERS	
BROTHERS	
SISTERS	
PATERNAL AUNTS	
PATERNAL UNCLES	
MATERNAL AUNTS	
MATERNAL UNCLES	

Now, I will be asking about all of your relatives who have been diagnosed with cancer and those that have not had cancer. **(Names are optional if given and are for identification during interview only.)**

MOTHER'S INFORMATION

A9. Is your mother still living?

[ ] Yes (Name_____)
[ ] No, skip to A11.

A10. How old is your mother? ☐☐☐ **. skip to A12.**

A11. How old was your mother when she died? ☐☐☐

A12. Did your mother ever have breast cancer or ovary cancer?

[ ] YES, BREAST CANCER, ONE BREAST
[ ] YES, BREAST CANCER, BOTH BREASTS
[ ] YES, OVARY CANCER
[ ] NO
[ ] DON'T KNOW OR REMEMBER

A13. How old was she when it was first diagnosed?☐☐☐ (BREAST)
☐☐☐(OVARY)

A14. Did your mother ever have any other kind of cancer?
[ ] Yes
[ ] No, skip to A17

A15. What other kind of cancer(s) did she have?

a. _____

b. _____

A16. How old was she when it was diagnosed?

a. ☐ ☐ ☐

b. ☐ ☐ ☐

FATHER'S INFORMATION

A17. Is your father still living?
[ ] Yes
[ ] No, SKIP TO A19

A18. How old is your father? ☐☐☐ SKIP TO A20

A19. How old was your father when he died? ☐☐☐

A20. Did your father ever have cancer?
[ ] Yes
[ ] No, skip to A23

A21. What kind of cancer(s) did he have?

a. _____

b. _____

c. _____

d. _____

A22. How old was he when it was diagnosed?

a. ☐ ☐ ☐

b. ☐ ☐ ☐

c. ☐ ☐ ☐

d. ☐ ☐ ☐

Let's continue with your sisters and brothers, both living and deceased.

SISTER'S INFORMATION

A23. Altogether, how many FULL sisters have you had? ☐☐ (Number)
[ ] None, or adopted

Sister's Inform.	Oldest sister		2nd sister		3rd sister		4th sister		5th sister	
A. 24 Is your (?) sister still living	yes	no go to A26	yes	no go to A26	yes	no go to A26	yes	no go to A26	yes	no go to A26
A. 25 How old is she?	Age		Age		Age		Age		Age	
A. 26 How old was she when she died?	Age		Age		Age		Age		Age	
A. 27 Did she ever have Breast Cancer or Ovary Cancer?	[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW	
A28 How old was she when it was first diagnosed?	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar
A29 Did she ever have any other kind of cancer?	yes	no	yes	no	yes	no	yes	no	yes	no
A30 What kind of cancer did she have?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A31 How old was she when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A32 Was she a twin or triplet?	yes	no	yes	no	yes	no	yes	no	yes	no
A33 If yes, was she an identical or fraternal twin, triplet?	ident	frat.	ident	frat	ident	frat	ident	frat	ident	frat

BROTHER'S INFORMATION

A34. Altogether how many FULL brothers have you had? ☐☐

Brothers' Inform.	Oldest brother		2nd brother		3rd brother		4th brother		5th brother	
A. 35 Is your (?) brother still living	yes	no go to A37	yes	no go to A37	yes	no go to A37	yes	no go to A37	yes	no go to A37
A. 36 How old is he?	Age		Age		Age		Age		Age	
A. 37 How old was he when he died?	Age		Age		Age		Age		Age	
A. 38 Did he ever have Cancer?	[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW	
A39 What kind of cancer did he have? Types:	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Types:	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A40 How old was he when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Age	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A41 Was he a twin or triplet?	yes	no	yes	no	yes	no	yes	no	yes	no
A42 If yes, was he an identical or fraternal twin, triplet?	ident	frat.	ident	frat	ident	frat	ident	frat	ident	frat

TWIN INFORMATION

A43. Are you a twin?
[ ] Yes
[ ] No, skip to A4?

A44. Which brother or sister is your twin?
[ ] Brother #☐, skip to A46
[ ] Sister #_

A45. Are you identical twins?
[ ] Yes
[ ] No
[ ] Don't Know

MOTHER'S SIDE OF FAMILY

Now I have some questions about other relatives. I will begin with your mother's parents and her side of the family.

A46. First, was your mother adopted?
[ ] Yes, skip to A77
[ ] No
[ ] Don't Know

Mother's Mother (Maternal Grandmother)

A47. Is your mother's mother still living?
[ ] Yes
[ ] No, Skip to A49

A48. How old is your mother's mother? _____Skip to A50

A49. How old was your mother's mother when she died? ___

A50. Did your mother's mother ever have breast cancer or ovary cancer?

[ ] Yes, breast cancer, one breast
[ ] Yes, breast cancer, both breasts
[ ] Yes, ovary cancer
[ ] No
[ ] Don't Know

A51. How old was she when it was first diagnosed?

____ (Breast)
____ (Ovary)

A52. Did your mother's mother ever have any other kind of cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A53. What kind of cancer(s) did she have?=======A54. How old was she when it was diagnosed?

a._____ a.____
b._____ b.____
c._____ c.____

Mother's Father (Maternal Grandfather)

A55. Is your mother's father still living? [ ] Yes
[ ] No

A56. How old is your mother's father? ____

A57. How old was your mother's father when he died? ____

A58. Did your mother's father ever have have cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A59. What kind of cancer(s) did he have?==A60. How old was he when it was diagnosed?

a._____ a.____
b._____ b.____
c._____ c.____

Now I will ask you about your mother's brothers and sisters, both living and deceased.

Mother's Sisters (Maternal Aunts)

A61. Altogether, how many FULL sisters or did your mother have? ____ (Number)
[ ] None

Mother's Sisters.	Oldest sister		2nd sister		3rd sister		4th sister		5th sister	
A62 Is her (?) sister still living	yes	no go to A64	yes	no go to A64	yes	no go to A64	yes	no go to A64	yes	no go to A64
A63 How old is she?	Age		Age		Age		Age		Age	
A64 How old was she when she died?	Age		Age		Age		Age		Age	
A65 Did she ever have Breast Cancer or Ovary Cancer?	[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW	
A66 How old was she when it was first diagnosed?	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar
A67 Did she ever have any other kind of cancer?	yes	no	yes	no	yes	no	yes	no	yes	no
A68 What kind of cancer did she have?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A69 How old was she when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.

Mother's Brothers (Maternal Uncles)

A70. All together how many full brothers did your mother have? _____(Number)
_____None

Mother's Brothers	Oldest brother		2nd brother		3rd brother		4th brother		5th brother	
A71 Is your (?) mother's brother still living	yes	no go to A73	yes	no go to A73	yes	no go to A73	yes	no go to A73	yes	no go to A73
A72 How old is he?	Age		Age		Age		Age		Age	
A73 How old was he when he died?	Age		Age		Age		Age		Age	
A74 Did he ever have Cancer?	[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW	
A75 What kind of cancer did he have? Types:	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Types:	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A76 How old was he when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Age	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.

Now I have some questions about your father's parents and his side of the family.

A77. First, was your father adopted?

[ ] Yes, skip to A108
[ ] No
[ ] Don't Know

Father's Mother (Paternal Grandmother)

A78. Is your father's mother still living?

[ ] Yes
[ ] No

A79. How old is your father's mother? ___

A80. How old was your father's mother when she died? ___

A81. Did your father's mother ever have breast cancer or ovary cancer?

[ ] Yes, breast cancer, one breast
[ ] Yes, breast cancer, both breasts
[ ] Yes, ovary cancer
[ ] No
[ ] Don't Know

A82. How old was she when it was first diagnosed?

____ (Breast)
____ (Ovary)

A83. Did your father's mother ever have any other kind of cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A84. What kind of cancer(s) did she have?

a._____
b._____
c._____

A85. How old was she when it was diagnosed?

a.____
b.____
c.____

Father's Father (Paternal Grandfather)

A86. Is your father's father still living?

[ ] Yes
[ ] No

A87. How old is your father's father? ___

A88. How old was your father's father when he died? ___

A89. Did your father's father ever have have cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A90. What kind of cancer(s) did he have?===**A91. How old was he when it was diagnosed?**

a._____ a._____
b._____ b._____
c._____ c._____

Now I will ask you about your father's brothers and sisters, both living and deceased.

Father's Sisters (Paternal Aunts)

A92. Altogether, how many FULL sisters or did your father have? ____ (Number)
[ ] None

Father's Sisters.	Oldest sister		2nd sister		3rd sister		4th sister		5th sister	
A93 Is his (?) sister still living	yes	no go to A95	yes	no go to A95	yes	no go to A95	yes	no go to A95	yes	no go to A95
A94 How old is she?	Age		Age		Age		Age		Age	
A95 How old was she when she died?	Age		Age		Age		Age		Age	
A96 Did she ever have Breast Cancer or Ovary Cancer?	[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW	
A97 How old was she when it was first diagnosed?	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar
A98 Did she ever have any other kind of cancer?	yes	no	yes	no	yes	no	yes	no	yes	no
A99 What kind of cancer did she have?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A100 How old was she when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.

Father's Brothers (Paternal Uncles)

A101. Altogether, how many FULL brothers did your father have?_____(Number)
[ ] None

Father's Brothers	Oldest brother		2nd brother		3rd brother		4th brother		5th brother	
A102 Is your (?) father's brother still living	yes	no go to A104	yes	no go to A104	yes	no go to A104	yes	no go to A104	yes	no go to A104
A103 How old is he?	Age		Age		Age		Age		Age	
A104 How old was he when he died?	Age		Age		Age		Age		Age	
A105 Did he ever have Cancer?	[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW	
A106 What kind of cancer did he have? Types:	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Types:	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A107 How old was he when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Age	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.

Now I would like to ask questions about your children. Not adopted children, but your natural children.

Sons

A108. How many sons do you have? Natural sons, not adopted. _____ (Number)

Sons' Inform.	Oldest son		2nd son		3rd son		4th son		5th son	
A109 Is your (?) son still living	yes	no go to A111	yes	no go to A111	yes	no go to A111	yes	no go to A111	yes	no go to A111
A110 How old is he?	Age		Age		Age		Age		Age	
A111 How old was he when he died?	Age		Age		Age		Age		Age	
A112 Did he ever have Cancer?	[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW		[ ] Yes [ ] No [ ] DON'T KNOW	
A113 What kind of cancer did he have? Types:	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Types:	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A114 How old was he when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
Age	c.	d.	c.	d.	c.	d.	c.	d.	c.	d.
A115 Was he a twin or triplet?	yes	no	yes	no	yes	no	yes	no	yes	no
A116 If yes, was he an identical or fraternal twin, triplet?	ident	frat	ident	frat	ident	frat	ident	frat	ident	frat

Daughters

A117. How many daughters do you have? Natural daughters, not adopted. _____

Daughter's Inform.	Oldest daughter		2nd daughter		3rd daughter		4th daughter		5th daughter	
A118 Is your (?) daughter still living	yes	no go to A120	yes	no go to A120	yes	no go to A120	yes	no go to A120	yes	no go to A120
A119 How old is she?	Age		Age		Age		Age		Age	
A120 How old was she when she died?	Age		Age		Age		Age		Age	
A121 Did she ever have Breast Cancer or Ovary Cancer?	[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW		[ ] Yes, one breast [ ] Yes,both breast [ ] Yes ovary [ ] No [ ] DON'T KNOW	
A122 How old was she when it was first diagnosed?	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar	Brst	Ovar
A123 Did she ever have any other kind of cancer?	yes	no	yes	no	yes	no	yes	no	yes	no
A124 What kind of cancer did she have?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A125 How old was she when it was diagnosed?	a.	b.	a.	b.	a.	b.	a.	b.	a.	b.
A126 Was she a twin or triplet?	yes	no	yes	no	yes	no	yes	no	yes	no
A127 If yes, was she an identical or fraternal twin, triplet?	ident	frat.	ident	frat	ident	frat	ident	frat	ident	frat

COUSINS

A128. Do you have any cousins on your **father's** side of the family who have been diagnosed with cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A129. Which of the following types of cancer have occurred in any of your cousins on your **father's** side of the family?

CANCER	OCCURRED
BREAST	
OVARY	
PROSTATE	
COLON	
OTHER_____	

A130. Do you have any cousins on your **mother's** side of the family who have been diagnosed with cancer?

[ ] Yes
[ ] No
[ ] Don't Know

A131. Which of the following types of cancer have occurred in any of your cousins on your **mother's** side of the family?

CANCER	OCCURRED
BREAST	
OVARY	
PROSTATE	
COLON	
OTHER_____	

APPENDIX 3. AGENDA, CALGB *Ad Hoc* COMMITTEE ON POLICY FOR GENETIC RESEARCH IN CLINICAL CANCER TRIAL PATIENTS.

Agenda

CALGB *ad hoc* Committee on Policy for Genetic Research in Clinical Cancer Trial Patients

Sheraton Crystal City Hotel
Arlington, VA
September 14, 1994, 8:00 a.m. - 4:00 p.m.

Participants:

Jeffrey Abrams
Maurice Barcos
Daniel Budman
Debrah Collyar
Lynne Dressler
Helen Felsenthal
Leslie Ford
Judy Garber
Stephen George
Elizabeth Hart
Alice Kornblith
Patricia Kvochak
Fred Li
Edison Liu
Alvin Mauer
Robert Mayer
Ross McIntyre
Robert Milliken
Susan Moore
Joan Porter
Karen Sartell
Natalie Davis Spingarn
Ellen Stovall
Elizabeth Thompson
Vincent Vinciguerra

I. Distinction between somatic DNA genetic research and germline DNA genetic research - differential impact on patient and family

II. Informed Consent
- A. Germline DNA studies
  1. Considerations of Phase I, II, III studies
  2. Stored samples
- B. Somatic DNA Studies
  1. Retrospective studies
  2. Prospective studies

III. Confidentiality
- A. Protections from third party access (government, insurance)
- B. Sample identification
- C. Oversight committee

IV. Responsibility to patient and family members - results disclosure, follow-up and counseling

V. Ownership of tissues

VI. Other

APPENDIX 4. MEMO TO CALGB INVESTIGATORS CONTAINING INFORMATION FOR IRBS

INFORMATION TO BE PROVIDED TO YOUR IRB FOR REVIEW OF CALGB PROTOCOL 9484.

This protocol raises issues in areas where IRBs have not yet had much experience. Our intention to study familial cancer genes is viewed as positive by the cancer patient advocacy groups who have participated in the design of this study. Several such groups and the Congress are interested in legislation that would further protect the confidentiality of this type of information and the field is rapidly evolving. This memo summarizes questions that have come up during the review of the protocol at various institutions and provides answers to these questions. It should be used as a supplement to other information you provide to your local research committees and to your IRBs.

Questions and Answers

Question: *Must my institution have an approved genetic counseling program before the protocol can be activated?*

Answer: No. It is necessary, however, for your institution to intend to develop a means of providing genetic counseling to patients entered on this protocol if they are to receive the results of testing for familial cancer genes. CALGB plans workshops and other training opportunities to assist institutions in developing counseling. Institutions may choose to refer patients for genetic counseling to other institutions, when appropriate.

Question: *When will results from tests performed in 9484 be available and when will the above counseling need to be available?*

Answer: The first results from this protocol are not expected before 1998-99.

Question: *My institution/committee believes that it is inappropriate to furnish research results from 9484 to patients. May our institution still participate in 9484?*

Answer: Yes. In this case, your institution would adapt the first model consent in the protocol for approval in your institution explaining within it that it is not planned to communicate the results of this testing to the patient. The second model consent, having to do with permission to inform the patient of the results would not be used in this situation.

Question: *If the patient refuses to give consent for studies of familial cancer genes and our institution has approved such studies as part of the protocol may the patient still participate in CALGB 9484?*

Answer: Yes. Tissue blocks, plasma and urine may still be obtained according to CALGB 9484 as well as the additional history.

Question: *How does CALGB maintain confidentiality concerning the results of this genetic research? Who will have access to patient-linked research data?*

Answer: Access to information from CALGB clinical trials is governed by procedures defined in the CALGB Policy and Procedure Manual and in the documentation of the CALGB data-base. These policies and procedures have been established to protect the confidentiality of the information collected on our study patients. Specifically, access to the CALGB data-base for 9484 (and the clinical trials from which patients entered on 9484 will be derived) is limited to the two statisticians assigned to 9484. Only these individuals will be able to link the special laboratory studies (for instance, familial cancer gene tests) with other information about the patient. There is no need for the study chair or anyone else to have access to information linked to identified patients. Clinical Research Associates at the Data Management Center under supervision by the

Research Associates at the Data Management Center under supervision by the statisticians will enter information on each patient. When data entry occurs, for instance concerning the presence of a familial cancer gene, the procedures used protect this information from discovery by others.

Auditors from the CALGB visit CALGB institutions to verify clinical data. In the course of such audits, they will need to know that patients entered on CALGB clinical breast cancer trials have also been entered on CALGB 9484. They will not have access to the results of laboratory tests carried out on specimens derived from 9484, however.

Your committee should understand that, if the patient requests it, information concerning the presence or absence of cancer risk genes may be communicated by CALGB to the patient's physician so that the patient may be informed of test results (with appropriate counseling). Each institution and physician is responsible for establishing its own procedures to receive and communicate this information in a manner that will prevent discovery. If it is placed in the medical record, for instance, it will generally be subject to discovery.

Question: *What methods should be used to ensure confidentiality at our institution?*

Answer: That is up to you and your institution to decide. CALGB cannot specify methods that will be acceptable to all institutions. For example, however, if the notification from CALGB to the institutional physician was never duplicated or abstracted in the medical record and if it were given at the counseling session to the patient for retention or destruction, this would assist in preservation of confidentiality. Results from commercial genetic tests will be available shortly and institutions are going to have to develop policies on this regardless of the research performed on CALGB 9484. It should be mentioned that increasingly the traditional relationship between the physician and the patient may be altered by contractual relationships between HMOs and/or industry and the physician. Only those responsible for this project at each institution will fully understand these local relationships and be able to develop methods whereby the interests of the patient who participates in 9484 are protected.

Question: *How can CALGB guarantee that insurers/employers will not ask for the results of this testing?*

Answer: A reading of the consent form will demonstrate that we try to inform the patient of the risk that an insurer/employer, etc. might ask for this information. CALGB is in no position prevent a potential employer/insurer from asking for this type of information. If the patient signs a form for an insurer or employer giving permission for access to her medical records, and if the institution has put the CALGB derived information in the medical record, it will then be available to the insurer/employer. We urge institutions to develop procedures whereby this type of information does not appear in the medical record.

Your committee should be reassured by recent events in another cooperative group. In this case, an insurer obtained a subpoena requiring that the cooperative group furnish information from its database. This subpoena was quashed on appeal by the cooperative group.

The wording of the model consent, our view, adequately informs the patient of the preliminary nature of the tests being used, indicates that they may not be approved by the FDA, etc. and states that they require confirmation, when possible.

Question: The protocol mentions possible tests and questionnaires on family members. It doesn't go into sufficient detail on these tests. Why?

Answer: Studies on relatives are described in the protocol so that if we are able to obtain funding for studies on relatives that they can be implemented expeditiously. At the present time, no studies of relatives will be undertaken. Who will be asked, and how, will depend upon whether funds are obtained, how much funding is obtained, and the conditions under which a granting agency awards the funds. We wished patients who consent to 9484 to understand that CALGB has an interest in studies of family members, and to be informed that such studies might be developed.

Question: *Who owns the tissue blocks on these patients?*

Answer: The "ownership" issue has not been resolved, although various parties quote legal opinions as to who "owns" the tissue. As long as the patient, and the patient's institution, and the laboratory doing the study all agree that the tissue should be studied, the issue goes away. This is what we are trying to accomplish in CALGB 9484- an agreement between the first two parties. The third is the subject of a letter of agreement between the receiving laboratory and the CALGB. This gets the research started now rather than awaiting what may ultimately be a Supreme Court decision.

Question: *Couldn't genomic DNA be recovered from normal tissue adjacent to the tumor and be used to determine the presence or absence of a familial cancer gene?*

Answer: The consent does allow DNA testing on "normal" tissue adjacent to tumor tissue. However, findings on such tissue will not be regarded by CALGB as representing "genomic" DNA. Such studies will not be used to attribute "familial" cancer genes to an individual.

Question: *The tests that may be applied to these specimens are too broadly defined. My IRB wishes to have a new consent each and every time a new test is proposed for application to the specimen.*

Answer: The model consent form clearly states (p17) that the research will be "limited to studies on cancer genes". If the committee is unwilling to accept the procedures established by CALGB for peer review and prioritization of the various future uses of the specimens, then it shouldn't approve 9484 and your institution should not participate. It is not CALGB's intention to get into a situation where every new use of a specimen must receive a new review and approval by our 200 separate IRBs, the patient re consented, etc. This is impractical. The patient advocacy community supports us strongly in this position.

Question: *A Certificate of Confidentiality is mentioned in the protocol. What is the status of this?*

Answer: At the present time, CALGB has not received a Certificate of Confidentiality covering this project. The multi institution character of the research has represented a novel situation for HHS in this regard and HHS has not acted upon our request. I believe that we will ultimately be successful. We will inform the members as soon as we receive the certificate, but at present a we do not have it. A statement to this effect could be placed in the consent according to your institutional desires.

Question: *Our institution objects to the disclaimer required by the Department of Defense. (You are authorized all necessary medical care for injury or illness which is the proximate result of your participation in this research.) We would like to use the standard language included in our consents for NIH grants. Can the language in this section of the model consent for 9484 be changed?*

Answer: Unfortunately the answer is no. Extensive efforts to have this clause removed from our Notice of Award from the Department of Defense (DOD) were unsuccessful.

The disclaimer statement is required by the Department of Defense (DOD) which is supporting this research.

Fortunately, it will be noted that this is not a treatment protocol. The patients receive no therapy as a result of their participation in CALGB 9484 and the specimens that are the subject of the research are obtained in the ordinary course of diagnosis and treatment. The risks to the patient are those of having a blood sample taken (at the time other blood samples are being taken for diagnostic or treatment purposes) and having a urine sample collected. The financial risk to the institution is therefore limited to "providing all necessary medical care for injury or illness which is the proximate result" of whatever additional risk is represented by the collection of the research specimen during these extremely low risk procedures carried out for treatment purposes.

The tangible risk to the participants involved in this research is not from treatment but rather that they might be discovered to possess a familial cancer gene and that this information about them could be discovered by an insurer or potential employer. CALGB believes that it has taken appropriate steps to reduce this risk to a minimum, and will convey any such information to its physician members, only if genetic counseling is available at the institution and the patient has expressed a desire to know the results of this testing. It is asking its member institutions to develop means of conveying this information to those patients desirous of knowing the results in a manner that prevents the loss of confidentiality.

I suppose it is conceivable that a patient who was desirous of knowing the result of a laboratory test could later claim that this information was the cause of a depression that would lead to hospitalization and that the patient could demand the provision of care for this without charge by the institution. It is my understanding that the "proximate cause" has not been established when this type of claim has been tested in other somewhat analogous situations.

I believe the procedures developed by CALGB for the conduct of the study, the wording of the model consent form, and the requirement that this study be activated only in institutions that can provide results to the patient with adequate genetic counseling, sufficiently minimize the risk to the institution so that the study should be approved.

Question: *The model consent form includes a place for the name of an IRB member the patient may contact. We feel this is inappropriate.*

Answer: The content of the consent form with the exception of the statements concerning risk/benefits and alternatives is a matter for the institution to decide. You are free to delete the statement. I believe that it is a good idea to list a person other than the patient's physician who can be contacted by the patient, if desired. In this way the institution is protected to some degree from charges of coercion if questions ever arise.

Question: *Our IRB quotes federal regulations that state "No informed consent...may include any exculpatory language through which the subject ...is made to waive or appear to waive any of the subject's legal rights..." The consent in which the patient gives away the right to a future interest in discoveries from use of the specimens may violate this regulation.*

Answer: This topic was extensively discussed by the project participants, members of cancer patient advocacy groups, representatives of OPRR, NCI legal counsel, and the CALGB leadership during a 1994 meeting. A summary of this meeting is available for IRBs to review, if needed. Instructions for obtaining it are given in a column on page 7 in the winter, 1995 CALGB Newsletter (volume 4, number 4). In short, CALGB and the patient advocacy community does not believe that the separate model consent form offered in 9484 in which the patient gives away these rights is either exculpatory or coercive. A patient may still participate in 9484 if this separate model consent is not signed. Many of us, including the those who have worked with us in the advocacy community believe that a person may give a generalized permission for use of

tissue or blood specimen. This is done every time a person gives blood during a blood donation drive. Nor do we believe that a person can be prohibited from making a donation in which certain rights are waived if the person wishes to waive those rights.

APPENDIX 5. CALGAB NEWSLETTER, VOLUME 4, NUMBER 4,WINTER 1995, PAGE 7

Procurement Of Specimens and Additional Historical Information From Breast Cancer Patients - CALGB 9484 and 9580

by O. Ross McIntyre, M.D., Dartmouth-Hitchcock Medical School

The next significant advances in the treatment of breast cancer may come from the use of new methods to assign adjuvant treatment. Although adjuvant treatment prolongs the disease-free interval and survival for breast cancer patients overall, it is not equally effective for all patients–some would remain disease free without the treatment, and others who receive it will have early recurrence in spite of it. With new knowledge coming from the application of molecular genetic methods to the analysis of breast cancer tissue, we anticipate that we can better predict who will and who will not benefit from the several types of adjuvant therapy that are available. In fact, studies performed on tissue specimens from patients randomized to CALGB 8541 (Adjuvant CAF for Pathologic Stage II Node + Breast Cancer) suggest that it may be possible to identify those patients who will not benefit from higher dose adjuvant regimens containing doxorubicin.

It is important to see if this observation can be confirmed, to expand molecular genetic studies as rapidly as possible, and to identify other indicators that will help determine what type of adjuvant therapy should be given and who should receive it. Two protocols describe the collection of tissue, blood, and urine samples. CALGB 9484 governs the collection of tissue specimens in addition to the collection of blood cells that will be used to detect familial genes. Such genes in "cancer families" predispose some patients to cancer. For this type of study, special consideration is given to informed consent issues, and the CALGB has specified that institutions must have genetic counseling or plans to develop genetic counseling before entering patients on 9484. A grant from the Army Research and Materiel Command supports this study, and $275 per registration is available to defray the costs of the study. Patients may be entered on 9484 whether or not they agree to have specimens collected for the purpose of identifying familial cancer genes.

For patients in institutions where genetic counseling is not available and which do not plan to offer genetic counseling in the future, CALGB 9580 will be available. This protocol also provides for the collection of tissue, blood, and urine samples, but tissue will be restricted to the study of somatic genetic changes (changes found only in the tumor cells and not passed on to offspring). (9580 does not include payments to cover the costs of specimen procurement.)

It is possible that the presence or absence of familial cancer genes will influence the course of the disease as well as the response to various treatments. We plan to integrate the information about the presence or absence of these genes with all the other clinical and treatment information we have concerning our patients. This is a particular strength of CALGB 9484. Datasets that merge information about tumor biology with carefully recorded staging information on breast cancer and with detailed information concerning the type and amount of treatment on large numbers of patients are not easily available. It is for this reason that this project received a high priority for funding during its scientific review.

In addition, protocols 9484 and 9580 collect additional information concerning family, reproductive, dietary, and exposure history, and psychosocial information that will be integrated into the CALGB database. For patients on 9484, information on these topics will be obtained from a telephone interview and a patient-completed questionnaire in order to ensure that complete and accurate information is recorded. These data will be used to explore questions involving the causes of breast cancer and to ascertain the impact of the genetic testing upon the patients.

The more rapidly we collect the specimens and dataset the more rapidly the large number of investigators who wish to use these resources can proceed with their research. We plan to collect 1,000 specimens with the help of the Army grant. Institutions may register patients to 9484 as soon as their IRBs have approved the protocol. The CALGB will be offering educational programs geared to assist institutions in developing genetic counseling capabilities. Because we expect commercial tests for familial cancer genes will be available soon, institutions need to develop the capacity to offer genetic counseling to their patients. The CALGB plans to help by providing appropriate education programs. We are collecting the names of individuals in CALGB institutions that have an interest in this area. If your institution has not answered the questions on a recently submitted form for this purpose, please do so. The sooner we know what your institutional plans are, the sooner we can develop appropriate educational activities.

Although protocol 9484 has been activated in many CALGB institutions, some IRBs have raised questions concerning the study. Because it is not currently possible to know what tests will be most informative on the specimens several years from now, we ask that the patient give permission for unspecified cancer-related tests on these specimens in the future. Such testing will be reviewed by the IRBs at the institutions where the investigators performing the research are located. Some IRBs have taken the position that each individual type of test must be reviewed every time a new test is added to those that are under way. The CALGB has introduced additional procedures to review the proposed use of the specimens and to assign priority to those studies that are most likely to advance the field. When this aspect of our study was under development, an ad hoc meeting of a diverse group of experts assisted in the development of the consent form and procedures for study review. A summary of this meeting, which included geneticists, oncologists with breast cancer expertise, representatives of cancer patient advocacy groups, lawyers, Office for Protection From Research Risks (OPRR), and others, is available, if necessary, to support the review of 9484 or 9580 in your institution. In addition, this position has been reviewed and approved by the NCI. Please contact the Central Office for copies of materials from these meetings that may assist your institution's IRB with the review of these protocols, if necessary.

APPENDIX 6. CONSENT FORM ISSUES HAMPERING ACCRUAL TO CALGB PROTOCOL 9484

MEETING SUMMARY: LINKED REGISTRY STEERING COMMITTEE JUNE 2, 1997

Wording required in consent forms: The protocol covering the activities of the Registry, CALGB 9484, had been amended at the request of the investigators and institutions so that the consent form for investigational treatment and that for participation in the Registry were combined. This resulted in a significant increase in efficiency at our institutions. However, the Office for Protection from Research Risks (OPRR) of the NIH found that language required by the Army concerning the donation of specimens was "exculpatory" and indicated that it would not approve the combined model consent form. The Steering Committee recommended that the Principal Investigator and his colleagues attempt to resolve this issue. Several phone calls and letters to the parties involved failed to eliminate the impasse and at present CALGB is preparing its new adjuvant treatment protocol with two separate consent forms in order to satisfy a review by the parties funding the treatment and Registry functions respectively. As a result there will be various inefficiencies at the institutional level and it is likely that the accrual to 9484 will decline somewhat from its current level of 10 per month.

We have suggested to the Army that the language concerning the donation of the tissue and fluids be changed to the following: "**In signing this consent form I donate the blood, urine and tissue samples that will be obtained from me to the Cancer and Leukemia Group B for the purposes of the research described in this consent form. The project staff, supported by a contract from the U.S. Army Research and Materiel Command to Dartmouth College, will use these samples exclusively for the research described above.**" We understand that this wording is not perceived as exculpatory by OPRR.

In addition, it is reasonable to assign a negligible risk to having a blood sample drawn for our project at the same time a blood sample is being obtained for routine blood work. Completing a telephone administered questionnaire is also a negligible risk. For this reason we have proposed dropping the phrase required by the Army stating that the contractor will "support the cost of medical care should illness from participating in this protocol occur". IRBs do not understand that Dartmouth College is the contractor, not their institution, and that Dartmouth has accepted this risk as the contractor. We are told that the consent forms are referred to institutional counsels who, lacking background in this matter, suggest non-approval. **We recommend dropping this statement from the consent forms for our 200 institutions, since it is not relevant to the type of research being supported.**

ACCEPTANCE OF THESE CHANGES BY THE ARMY COULD RESULT IN IMPROVED ACCRUAL.

APPENDIX 7. CALGB PROTOCOL 9484

Status Notice
7/15/99

CANCER AND LEUKEMIA GROUP B

CLOSURE OF CALGB 9484

LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

_____**Revision** ____**Amendment**	**_X_ Status Change**
_____Change of participants/coordinator (s) +/-	____Activation
_____Editorial, administrative changes	_X_ Closure
_____Scientific changes (IRB approval)	____Partial Closure
_____Therapy changes (IRB approval)	____Temporary Closure
_____Eligibility changes (IRB approval)	____Reactivation
_____Informed Consent changes (IRB approval)	
_____Other:	

Effective September 1, 1999 at 5:00 pm ET, this study is permanently closed to further accrual. All samples should be shipped no later than September 30, 1999. After 9/30/99, the Federal Express account will be invalid, and no further samples should be sent for patients registered to this study.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

cc: O. R. McIntyre, M.D.; D. F. Hayes, M.D.; D. Sandler, Ph.D.; B. Smith, M.D.; D. Berry, Ph.D.; R. Millikan, DVM, Ph.D.; D. McDonald, M.S.

Update #3
12/15/98

CANCER AND LEUKEMIA GROUP B

PROTOCOL UPDATE TO CALGB 9484

LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

__X__ **Revision** ____ **Amendment**	____ **Status Change**
_____Change of participants/coordinator (s) +/-	____Activation
__X__Editorial, administrative changes	____Closure
_____Scientific changes (IRB approval)	____Partial Closure
_____Therapy changes (IRB approval)	____Temporary Closure
_____Eligibility changes (IRB approval)	____Reactivation
_____Informed Consent changes (IRB approval)	
_____Other:	

REVISIONS:

Cover page: CALGB 9840 has been added to the list of studies to which CALGB 9484 is a companion.

Section 4.1: CALGB 9840 has been added to the list of eligible studies.

Section 8.4.3: The address for shipment of whole blood samples to the UNC DNA Extraction Laboratory has been updated.

Please note that urine should NOT be collected or shipped at this time. You will be notified when urine collection will begin.

Replacement pages: Cover page, p. 3-4, 9-10.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

cc: O. R. McIntyre, M.D., D. F. Hayes, M.D., D. Sandler, Ph.D., B. Smith, M.D., D. Berry, Ph.D., R. Millikan, DVM, Ph.D., D. McDonald

CANCER AND LEUKEMIA GROUP B

MEMORANDUM

To: Principal Investigators, CCOP Responsible Investigators, Disease and Modality Chairs, Executive Committee, Data Management Center, Statistical Center, QARC

From: Kathleen S. Karas, Senior Protocol Editor

Subject: **CALGB 9484: Forms C-383, C-384, C-449, and C-490**

Date: June 15, 1998

Attached please find revised versions of Forms C-383, C-384 and C-449 for CALGB 9484. Please replace previous versions of these forms with those attached. In addition, please replace Form C-350 in the appendix with the attached Form C-490, Tracking Form (Tissue Blocks).

Please note that urine samples are not being collected at this time; you will be notified when urine collection is to commence.

If you have questions regarding these forms, please contact Dana McDonald, Data Coordinator, at 919-286-0045, x235.

cc: O. Ross McIntyre, M.D., D. McDonald

Update #2
5/15/98

CANCER AND LEUKEMIA GROUP B

PROTOCOL UPDATE TO CALGB 9484

LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

X Revision	**X Amendment**	**Status Change**
X Change of participants/coordinator (s) +/-		___Activation
X Editorial, administrative changes		___Closure
_____Scientific changes (IRB approval)		___Partial Closure
_____Therapy changes (IRB approval)		___Temporary Closure
_____Eligibility changes (IRB approval)		___Reactivation
X Informed Consent changes (IRB approval)		
_____Other:		

Cover page: Dana McDonald replaces Laura Gross as data coordinator. Phone and fax numbers for Dr. Berry have been updated. CALGB 9741 has been added to the list of studies to which CALGB 9484 is a companion.

Section 4.1: CALGB 9741 has been added to the list of eligible studies.

Section 4.2: The statement that patients must initial the consent form has been replaced with "patients must indicate their agreement by circling yes or no on the consent form".

Section 5.0 Registration: The question "Does patient release or retain rights to specimens" has been removed.

Section 8.5 Shipment billing: Pre-printed Federal Express labels are no longer available. Instructions should continue to use the Federal Express account number provided by the Central Office when filling out shipment labels.

Section 10.0 Model Consent: A new model consent form is provided which may be used in place of the previously issued consent form. This simplified consent is based on a model for tissue procurement developed by the National Breast Cancer Coalition with input from various agencies, including the National Cancer Institute, and has been approved by the Department of Defense for use with this study. This model may either be combined with the treatment consent or used as a separate document at the discretion of the participating institution.

Please note that urine should NOT be collected or shipped at this time. You will be notified when urine collection should begin.

Replacement pages: Cover page, p 3-4, 9-10, 14-16.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

cc: O. R. McIntyre, M.D., D. F. Hayes, M.D., D. Sandler, Ph.D., B. Smith, M.D., D. Berry, Ph.D., R. Millikan, DVM, Ph.D., D. McDonald

CANCER AND LEUKEMIA GROUP B

MEMORANDUM

To: Principal Investigators, CCOP Responsible Investigators, Disease and Modality Chairs, Executive Committee, Data Management Center, Statistical Center, QARC

From: Kathleen S. Karas, Protocol Editor

Subject: **CALGB 9484: Forms C-383, C-384, C-449**

Date: March 15, 1997

Attached please find revised versions of Forms C-383 and C-384 for CALGB 9484. Please replace previous versions of these forms with those attached. In addition, Form C-449, Urine Sample Tracking Form, is provided. **Urine samples are not being collected at this time; you will be notified when urine collection is to commence.** Please insert Form C-449 in the appendices of CALGB 9484 for use once urine collection is initiated.

If you have questions regarding these forms, please contact Laura Gross, Data Coordinator, at 919-286-0045, x235.

cc: D. F. Hayes, M.D., D. Berry, Ph.D., C. Cirrincione, L. Gross

CANCER AND LEUKEMIA GROUP B

MEMORANDUM

To: Principal Investigators, CCOP Responsible Investigators, Disease and Modality Chairs, Executive Committee, Data Management Center, Statistical Center, QARC

From: Kathleen S. Karas, Protocol Editor

Subject: **CALGB 9484: Urine Specimens, Eligibility**

Date: November 15, 1996

IMPORTANT NOTICE

PLEASE DO NOT COLLECT OR SHIP URINE SPECIMENS FOR CALGB 9484 UNTIL FURTHER NOTICE.

Update #1 to CALGB 9484 issued 10/15/96 indicated that urine collection and shipment should begin. However, due to difficulties encountered in the processing of specimens, **please do NOT collect or ship urine specimens until notified** (via e-mail broadcast and/or protocol mailing notice). We expect these difficulties to be resolved shortly, and appreciate your patience in this matter. If you have any questions, please contact me (773-702-9674, kkaras@midway.uchicago.edu) or Dr. Hayes (202-687-2103, hayesdf@gunet.georgetown.edu).

PATIENT ELIGIBILITY FOR CALGB 8861, *Monitoring CA 15-3 Antigen During and After Adjuvant Therapy for Stage II, Node Positive Breast CA:*

Please note that if 9484 is active at your institution, you should **not** be entering a patient on both 8861 and 9484. New patients should be entered on 9484; only patients previously entered on 8861 (prior to activation of 9484 at your institution) should continue to have their samples submitted under 8861. If you have any questions, please contact me or Dr. Hayes.

cc: D. F. Hayes, M.D., D. Berry, Ph.D., C. Cirrincione, L. Gross

Update #1
10/15/96

CANCER AND LEUKEMIA GROUP B

PROTOCOL UPDATE TO CALGB 9484

LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

__X__Revision **__X_Amendment** **____Status Change**

__X__Change of participants/coordinator (s) +/-

__X__Editorial, administrative changes

__X__Scientific changes (IRB approval)

_____Therapy changes (IRB approval)

_____Eligibility changes (IRB approval)

__X__Informed Consent changed (IRB approval)

_____Other:

____Activation

____Closure

____Partial Closure

____Temporary Closure

____Reactivation

Due to the extensive changes made to this study, a replacement document is being issued at this time. Please discard the previous version of this protocol, including the model consent form. The appendices, however, should be retained, except for the following: replace the CALGB Detailed Family History and Epidemiology Telephone Interview in Appendix II with the updated version in this update, and add new Appendix IV, DHHS Confidentiality Certificate.

Note: The C-449 form for urine collection is not included in this mailing but will be issued in a subsequent mailing. If you need a C-449 form in the interim, please contact the CALGB Data Management Center, 919-286-0045, x221.

SUMMARY OF REVISIONS:

Address and phone numbers have been updated for Dr. McIntyre, Study Chair, Breast Committee Chair, Data Coordinator, and Dr. Hayes. ***PLEASE NOTE THAT ALL URINE AND BLOOD SHIPMENTS TO DR. HAYES SHOULD BE SENT TO LOMBARDI CANCER CENTER, NOT DANA FARBER CANCER INSTITUTE. EFFECTIVE WITH THIS UPDATE, URINE COLLECTION SHOULD BEGIN AS SPECIFIED IN THE PROTOCOL.***

The telephone area code for the Central Office has been changed; the fax number, however, remains the same.

Specimen procurement and shipping instructions have been clarified throughout the protocol.

The Department of Health and Human Services has issued a Confidentiality Certificate for this project; a copy is included as Appendix IV.

SUMMARY OF AMENDMENTS

Test results will no longer be provided to patients or their physicians. The tests conducted by the CALGB are intended for research, not diagnostic, purposes. Commercial tests are now available for those patients who wish to pursue this option after consultation with their physician. Since the results of research tests will no longer be provided to the institution, the requirement for comprehensive genetic counseling services has been dropped.

All references to registration of family members and studies of family members have been deleted, as these studies will not be pursued at this time.

There is no longer a free-standing consent form for 9484. Instead, the essential elements of consent for 9484 have been incorporated into the treatment protocol consent forms. The model consent sections are included in this protocol for reference only. Please see amendments dated 10/15/96 for protocols 9082, 9342, 9343, and 9344 and submit these revised treatment protocol consent forms to your IRB. Patients will be presented with all options included in the revised treatment consent form: collection of tissue, blood, urine, completion of questionnaires, and the separate section regarding the use of specimens to study heritable genes. Patients who agree to collection of tissue, blood, urine and the completion of questionnaires must initial these items within the treatment consent form as directed; patients who agree to have their specimens studied for heritable genes must sign the section of the treatment consent form entitled "Consent for Studies of Heritable (Familial) Cancer Genes". Registration to 9484 for those patients agreeing to these additional items should take place simultaneously with registration to the treatment protocol. Patients who agree to have their specimens collected, but refuse to have them studied for heritable genes, may still be entered on 9484. Questions regarding eligibility should be directed to the study chair, Dr. McIntyre, or to the Central Office (contact Kathleen Karas, protocol editor.)

This update contains Cover page through page 16, an updated CALGB Detailed Family History and Exposure Telephone Interview (Appendix II), and Appendix IV, DHHS Confidentiality Certificate.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

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cc: O. R. McIntyre, M.D., L. Norton, M.D., D. F. Hayes, M.D., D. Sandler, Ph.D., M. Barcos, M.D., L. Schnaper, M.D., D. Berry, Ph.D., L. Dressler, M.A., R. Millikan, DVM, Ph.D., L. Gross

Activation: June 15, 1995

CANCER AND LEUKEMIA GROUP B

LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

CALGB 9484

Companion to CALGB 9082, 9342, 9343, 9344, 9741, 9840

Study Chair
O. Ross McIntyre, M.D.
34 Lamphere Hill Lane
Lyme, NH 03768-3109
Tel: 603-795-2624 Fax: 603-795-2431
O.Ross.McIntyre@Dartmouth.edu

Breast Committee Chair
Larry Norton, M.D.
Tel: 212-639-6425 Fax: 212-717-3619
nortonl@mskcc.org

Correlative Science - Solid Tumor Chair
Daniel F. Hayes, M.D.
Phone: 202-687-2103 Fax: 202-687-4429
hayesdf@gunet.georgetown.edu

Epidemiology
Dale Sandler, Ph.D.
Tel: 919-541-4668 Fax: 919-541-2511
sandler@niehs.nih.gov

Pathology Chair
Maurice Barcos, M.D., Ph.D.
Tel: 716-845-4443 Fax: 716-845-8077
calgbpath@sc3102.med.buffalo.edu

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Tel. 919-681-5011 Fax: 919-681-8028
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Dana McDonald
Tel: 919-286-0045, x235 Fax: 919-286-1142
DMMcDonald@elephant.mc.duke.edu

Protocol Editor
Kathleen S. Karas
Tel: 773-702-9674 Fax: 312-345-0117
kkaras@midway.uchicago.edu

For questions regarding submission of tissue samples, contact:

Maurice Barcos, M.D.
CALGB Central Pathology Office
Roswell Park Cancer Institute
Department of Pathology
Elm at Carlton
Buffalo, New York 14263
Phone: (716) 845-4443 Fax: (716) 845-8077
calgbpath@sc3102.med.buffalo.edu

For questions regarding submission of whole blood samples, contact:

Lynn Dressler, M.A.
University of North Carolina
Medical Oncology Division
CB #7295 Lineberger Cancer Research Center
Chapel Hill, NC 27599-7295
Phone: (919) 966-0196 Fax: (919) 966-4244
dressler@med.unc.edu

For questions regarding submission of plasma and urine samples, contact:

Daniel F. Hayes, M.D.
Lombardi Cancer Center
Room E504
Research Building
3970 Reservoir Road, NW
Washington, DC 20007
Phone: 202-687-2103 Fax: 202-687-4429
hayesdf@gunet.georgetown.edu

For questions regarding forms, contact:

Dana McDonald
Data Coordinator
CALGB Data Management Center
First Union Plaza, Suite 340
2200 West Main Street
Durham, NC 27705
Tel: 919-286-0045, x235 Fax: 919-286-1142
DMMcDonald@ccstat.mc.duke.edu

For administrative issues, contact:

Kathleen S. Karas
Protocol Editor
CALGB Central Office
208 South LaSalle Street, Suite 2000
Chicago, IL 60604
Tel: 773-702-9674 Fax: 312-345-0117
kkaras@midway.uchicago.edu

TABLE OF CONTENTS

1.0 INTRODUCTION

This project involves the collection of tumor specimens, genomic DNA, and information concerning medical, reproductive, exposure and family history from patients with breast cancer. The purpose is to create a library in which clinical information on groups of uniformly staged and treated patients on CALGB protocols is located within a structure that also contains patient personal, family, and environmental exposure history, specimens from patients, and data from molecular and other laboratory studies. In contrast to a population-based tumor registry, it offers an internally cohesive group of patients with well-defined disease, treatment and follow-up. It will be possible to draw scientifically valid conclusions from this group by looking for interactions between treatment and factors such as genomic susceptibility and acquired somatic alterations.[1]

We have termed this resource a "specialized registry". The specimens (breast cancer tissue, plasma, urine, or in some cases, DNA) will be made available to qualified investigators who will conduct a variety of research projects that test laboratory-based, psycho-social or epidemiological hypotheses. These investigators will be supported by peer-reviewed grants and other mechanisms, and the studies will be done at no charge to patients. Laboratory results will be forwarded to the CALGB database where CALGB statisticians will be responsible for all analyses. All information resulting from these studies will reside in the CALGB database and all patient identifiers will remain confidential within the CALGB Data Management Center.

Population-based studies are not included at this time: with all of the ethical and legal ramifications inherent in population-based genetic studies, we feel that this type of study should come later when specific hypotheses are more fully formed and after we have established the scientific and psycho-social framework for communicating this type of information to the general public.

Ethical and legal issues relating to studies of heritable genes, and submission of tissue: Based upon policies adopted by the CALGB concerning studies of heritable cancer genes, a separate prospective informed consent for genomic DNA submission, as well as consent for participation in the other components represented, is required. These consent documents are incorporated into the consent documents for each relevant treatment protocol. Consent to participate in the specialized registry must be obtained at the time the patient enters the treatment study.

With respect to submission of fixed tissue blocks after diagnosis has been established at the local institution, there are a number of unresolved and sometimes conflicting issues that are currently being addressed by appropriate bodies. The "ownership" of the tissue blocks is felt by some to have been conveyed to the institution by the wording of the usual consent for surgery, but this is disputed by others who feel that, for the purposes represented by the studies to be performed via this protocol, the patient retains rights to the tissue. More particularly, the view has been expressed that the patient may have an enforceable privacy interest when studies are done on tissue that is linked in some manner to them.[3] We believe that the consent for the specialized registry included in each relevant treatment consent form specifies conditions in which the patient's right to privacy is not subjected to a new risk with each new use of the registry. State laws, the American College of Pathology, the Joint Commission on the Accreditation of Health Care Facilities, and the Clinical Laboratory Improvement Act (CLIA) may have requirements concerning retention of diagnostic tissue at the local institution, and it remains to be determined whether it is permissible under these policies to place the tissue in the custody of other approved parties. Finally, there are divergencies of opinion between the U.S. Army Medical Research and Materiel Command and the Office of Protection from Research Risks, National Institutes of Health, concerning a requirement that specimens collected with

funding from the Department of Defense become the property of the U.S. Government. Certain of these may require establishment of legal precedent for their resolution. Institutions with concerns about this possibly conflicting positions may wish to contact Dr. Maurice Barcos, Director of the CALGB Pathology Coordination Office, for additional information about the procedures that CALGB has established to ensure that fixed breast tissue remains available for return to the institution, if required.

2.0 OBJECTIVES

1. To collect formalin-fixed, paraffin-embedded (FFPE) breast tissue for in situ studies and extraction of somatic DNA and peripheral blood for extraction of germline DNA, also plasma and urine from patients with breast cancer entered on CALGB breast cancer treatment protocols.

2. To review and confirm the histopathological diagnosis of breast cancer on submitted tissue.

3. To gather key family, endocrine and reproductive history, and exposure data on the above patients.

4. To prepare and submit the above specimens to approved investigators who will perform various laboratory studies on them and provide the results to the CALGB database for correlation with clinical data and patient outcome.

5. To analyze the data resulting from the above activities in order to seek new knowledge about etiology and progression of breast cancer.

3.0 STATISTICAL CONSIDERATIONS

A Steering Committee is responsible for approving each individual project using the resources of the specialized registry. Each individual project submitted for review will contain a statistical section detailing the hypothesis and the estimated powers required in the proposed analyses. Flexibility is essential since the alternative hypothesis will vary from one project to the next. If the alternative hypothesis is close to the null, then a large number of patients will be required. A major element in the Steering Committee's review of the proposal will be whether the hypothesis may be adequately tested given the current resources of the registry.

Many of the proposals that we expect to receive will concern analyses of subgroups of patients within the registry. These would be conducted by evaluating an ordered list of scientific hypotheses using sequential statistical tests and would facilitate an early decision on whether a new hypothesis was worth further investigation, while avoiding wasting too much biological material on testing hypotheses that may eventually prove unfruitful. This method will also help to distinguish between a "multitude of hypotheses".[4] The value of the registry to the investigators will be enhanced if it is sufficiently large to allow them to test their hypotheses on subgroups of sufficient size so that adequate power is obtained to detect the differences which are sought. For this reason, the larger the number of patients represented in the specialized registry, the more useful the registry will be. It is anticipated that the alternative hypothesis will dictate power, and allocation of resources will proceed sequentially. There is a wealth of material on case only analyses, in which comparisons of cases only (no controls) are used to evaluate gene-environment interactions.[5] We have planned for a registry of up to 5,000 individuals but this number may be adjusted upwards or downwards without amending the protocol depending upon the experience with the various users and the ability to secure funds to operate the registry.

4.0 ELIGIBILITY CRITERIA

4.1 The patient must be enrolled on a CALGB breast treatment protocol. Those protocols from which patients may be entered are listed below. This list will be modified in updates (revisions) to this protocol to include additional CALGB adjuvant or metastatic breast cancer treatment protocols that are activated during the funding period.

9082 A Randomized, Comparative Study Of High Dose CPA/cDDP/BCNU and ABMS Versus Standard Dose CPA/cDDP/BCNU as Consolidation to Adjuvant CAF for Patients with Operable Stage II or Stage III Breast Cancer Involving 10 Axillary Lymph Nodes

9342 A Phase III Study of Taxol at Three Dose Levels in the Treatment of Patients with Metastatic Breast Cancer

9343 Evaluation Of Lumpectomy, Tamoxifen, and Irradiation of the Breast Compared with Lumpectomy Plus Tamoxifen in Women 70 Years of Age or Older Who Have Carcinoma of the Breast that is Less Than or Equal to 4cm and Clinically Negative Axillary Nodes: A Phase III Study

9344 Doxorubicin Dose Escalation, With Or Without Taxol, As Part Of The CA Adjuvant Chemotherapy Regimen For Node Positive Breast Cancer: A Phase III Intergroup Study

9741 A Randomized Phase III Trial of Sequential Chemotherapy Using Doxorubicin, Paclitaxel, and Cyclophosphamide or Concurrent Doxorubicin and Cyclophosphamide Followed by Paclitaxel at 14 or 21 Day Intervals in Women with Node Positive Stage II/IIIA Breast Cancer

9840 A Phase III Study of Paclitaxel Via Weekly 1 Hour Infusion Versus Standard 3 Hour Infusion Every 3 weeks in the Treatment of Patients with Metastatic Breast Cancer

4.2 Patients must indicate their agreement by circling yes or no on the consent form to have their archived tissue blocks, (including somatic DNA but excluding analyses of germline genetic characteristics on associated normal tissues), plasma, and urine submitted for study and to participate in collection of family, exposure and endocrine history questionnaires. Note: If the patient also consents to participate in genomic studies, cells for genomic DNA must be obtained prior to the first radiation or chemotherapy treatment.

5.0 REGISTRATION

Registration will be accepted through the Main Institution only. Confirm eligibility criteria (Sec 4.0). Call the CALGB Registrar (919-286-4704, Monday-Friday, 9 am-5 pm Eastern Time) with the following information:

Your name
Study #
Institution #
Treating Physician
Patient' s Social Security #
Patient' s Name, I.D.#
Patient's Address and Phone Number
Signed Informed Consent (Date)
Type of consent signed: Genomic studies, Non-genomic studies
Race, Sex, Date of Birth
Zip code of residence
Method of payment
Diagnosis, Date of Diagnosis
Eligibility Criteria met (Sec. 4.0) (yes, no)
List CALGB treatment protocol
Date of most recent Institutional Review Board approval (<1 year)

6.0 REQUIRED DATA

6.1 Submit data forms and specimens according to protocol requirements for all patients registered on CALGB 9484 who receive treatment on an appropriate CALGB breast treatment protocol.

6.2 CALGB institutions should submit specimens along with their corresponding pathology/specimen submission forms to the appropriate CALGB laboratory for storage, as indicated below. If tissue block will not be submitted for a patient, the institution should submit the CALGB Pathology Routing Form (C-350) indicating the reason for nonsubmission along with a letter from the institutional pathologist explaining the reason for nonsubmission.

Copies of these forms are included in this appendix.

6.2.1 Submit **tissue block** (or letter stating why tissue block will not be submitted), surgical path report and **original** C-350 form to:

Maurice Barcos, MD, PhD
CALGB Pathology Coordinating Office
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, NY 14263-0001

and a copy of C-350 form to the CALGB DMC; keep a copy for your records.

6.2.2 Submit **whole blood** specimens with **original** C-383 form to: **(NOTE: PATIENT MUST HAVE SIGNED CONSENT FOR STUDIES OF HERITABLE GENES)**

Daynice Skeen/Evangeline Reynolds/Lynn Dressler
UNC DNA Extraction Laboratory
University of North Carolina
CB #7304 Lineberger Cancer Research Center
112 MacNider Building
Chapel Hill, NC 27599-7305

and a copy of C-383 form to CALGB DMC; keep a copy for your records.

6.2.3 Submit **plasma** specimens with **original** C-384 form to:

Daniel F. Hayes, M D
Lombardi Cancer Center
Room E504
Research Building
3970 Reservoir Road, NW
Washington, DC 20007

and a copy of C-384 form to CALGB DMC; keep a copy for your records.

6.2.4 Submit **urine** specimens with **original** C-449 form to:

Daniel F. Hayes, M.D.
Lombardi Cancer Center
Room E504
Research Building
3970 Reservoir Road, NW
Washington, DC 20007

and a copy of C-449 form to CALGB DMC; keep a copy for your records.

6.2.5. Send Family History of Cancer Questionnaire to the CALGB DMC:

CALGB Data Management Center
2200 West Main Street, Suite 340
Durham, NC 27705

7.0 DATA SUBMISSION

FORM		Submission Schedule
C-350	CALGB Pathology Routing Form (for tissue blocks) Surgical path report	Submit both form and report regardless of whether or not block is sent. Submit with either tissue block from surgical specimen (breast or node) OR letter from pathologist stating reason for nonsubmission of block. Submit prior to first chemo/RT treatment.
C-383	CALGB Specimen Routing Form (for whole blood)	Submit with whole blood specimens. Submit prior to first chemo/RT treatment.
C-384	CALGB Specimen Routing Form (for plasma)	Submit with plasma specimen. Submit prior to first chemo/RT.
C-449	CALGB Specimen Routing Form (for urine)	Submit with urine specimen. Submit prior to first chemo/RT. For adjuvant studies using chemotherapy, submit prior to treatment, at the completion of treatment, and at each follow-up visit scheduled in the treatment protocol. For adjuvant studies using hormone therapy, submit prior to treatment and at each follow-up visit scheduled in the treatment protocol. For metastatic studies using chemotherapy, submit prior to treatment, on day one of each cycle, and at each follow-up visit scheduled in treatment protocol. For metastatic studies using hormone therapy, submit prior to treatment and at each follow-up visit scheduled in the treatment protocol.
C-377	Family History of Cancer Questionnaire	Within 2 wks of registration onto CALGB 9484. If the patient declines to complete the questionnaire, it should be submitted with "PATIENT DECLINED" and the date written across the top.

8.0 METHODS

8.1 ***Patient entry:*** Eligible patients are entered on this protocol if they consent at the time they are enrolled on the treatment protocol and meet study eligibility requirements given in section 4.0.

8.2 ***FFPE tissue:*** A representative block of the primary tumor is best for biologic markers and histologic correlations, but both primary and nodal tissues are acceptable for biologic assays. If insufficient primary or nodal tissue is available for submission of one block, a brief explanatory note from the institutional pathologist within six months of patient entry will suffice.

Submission of representative tissue sections on glass slides is not acceptable since the tissues must be processed in different ways for various assays: 4μ on glass slides for HE staining and immunohistochemistry, 10μ for DNA extraction, and 30μ for nuclear isolation for flow cytometry. The CALGB Pathology Office at Roswell Park Cancer Institute will prepare these sections as there is some evidence that antigen loss may occur over time on cut sections unless maintained at a low temperature.

Each submitted block will be carefully protected and monitored by the CALGB Pathology Office so that depletion of the block is minimized and a minimum of three recut HE sections remain on file at all times. National Institutes of Health directives call for the indefinite retention of each submitted block for future, as yet undetermined, biologic/genetic assays. Upon request for any emergent clinical or legal reason, the remaining portion of the block and one HE section will be returned by overnight mail to the originating Institutional Pathology Laboratory .

Tissue blocks from the operative (not needle biopsy) specimen along with the corresponding surgical pathology report and original Form C-350, CALGB Tissue Routing Form must be submitted to:

Dr. Maurice Barcos, Chair
CALGB Pathology Office
Roswell Park Memorial Institute
Department of Pathology
Elm and Carlton Streets
Buffalo, NY 14263
716-845-4443

Institutional data managers will arrange for submission of tissue blocks to the above address by contacting the appropriate pathologist at a CALGB main member or affiliate institution.

Somatic DNA: From the specimens collected as described above, individual investigators will prepare DNA according to their established laboratory procedures. It is anticipated that somatic DNA will be derived from the tumor specimen, but somatic DNA abnormalities may also be sought in normal tissue adjacent to the tumor.

8.3 Timepoints for collection of plasma, urine, and whole blood for genomic studies:

8.3.1 For Adjuvant studies using chemotherapy:

Collect whole blood for plasma and urine samples from patients prior to treatment initiation, at the completion of therapy, and at each follow-up treatment visit scheduled in the treatment protocol.

Collect whole blood separately for genomic DNA studies prior to treatment initiation only for those patients who have signed the portion of the consent form for studies of heritable cancer genes.

8.3.2 For Adjuvant studies using hormone therapy:

Collect whole blood for plasma and urine samples from patients prior to treatment initiation and at each follow-up treatment visit scheduled in the treatment protocol.

Collect whole blood separately for genomic DNA studies prior to treatment initiation only for those patients who have signed the portion of the consent form for studies of heritable cancer genes.

8.3.3 For Metastatic Studies using chemotherapy:

Collect whole blood for plasma and urine samples from patients prior to treatment initiation, on day one of each cycle of treatment, and at each follow-up visit scheduled for the treatment protocol.

Collect whole blood separately for genomic DNA studies prior to treatment initiation only for those patients who have signed the portion of the consent form for studies of heritable cancer genes.

8.3.4 For Metastatic Studies using hormone therapy:

Collect whole blood for plasma and urine samples from patients prior to treatment initiation and at each follow-up visit scheduled for the treatment protocol.

Collect whole blood separately for genomic DNA studies prior to treatment initiation only for those patients who have signed the portion of the consent form for studies of heritable cancer genes.

8.4 Collection and handling instructions for plasma, urine, and whole blood for genomic studies

8.4.1 Plasma collection and handling:

Collect 10cc of whole blood by venipuncture into an EDTA-containing (purple top) collection tube.

Centrifuge blood at 3000Xg for ten minutes (standard clinical centrifuge). Then aliquot supernatant plasma into a separate tube and label the tube with the patient's name, CALGB number, hospital number, the date of collection, the participating institution, and the number of the CALGB clinical protocol to which the patient is registered.

Separation (centrifuging, aliquoting) the plasma should be performed within 4-6 hours of collection. Samples may be stored at 4°C (regular ice, or regular refrigerator) for not more than 24 hours prior to storage at -20°C (a standard refrigerator freezer).

Both plasma and urine samples can be stored at -20°C at participating institution until several have accumulated. These samples can be mailed as batches (10-20 specimens or more) on dry ice overnight to the Lombardi Cancer Center at the address below. An original C-384 form must be submitted with each sample, with a copy of the form sent to the DMC.

Be certain that at least five (5) pounds of dry ice are used. Also, ship overnight express so that specimens will not arrive on a weekend or holiday. Address:

Daniel F. Hayes, M.D.
Lombardi Cancer Center
Room E504
Research Building
3970 Reservoir Road, NW
Washington, DC 20007
Telephone: 202-687-2103

8.4.2 Urine collection and handling:

Collect 50 ml (or more) clean catch urine into sterile urine collection container.

Centrifuge urine at 200g for 3 minutes (standard clinical centrifuge).

Pour spun urine into plastic freezing tube and label with the patient's name, CALGB number, hospital number, the date of collection, the participating institution, and the number of the CALGB clinical protocol to which the patient is registered.

Separation (centrifuging, aliquoting) the urine should be performed within 4-6 hours of collection. Samples may be stored at 4°C (regular ice, or regular refrigerator) for not more than 24 hours prior to storage at -20°C (a standard refrigerator freezer).

Both plasma and urine samples can be stored at -20°C at participating institution until several have accumulated. These samples can be mailed as batches (10-20 specimens or more) on dry ice overnight to the Lombardi Cancer Center at the address below. An original C-449 form must be submitted with each sample, with a copy of the form sent to the DMC.

Be certain that at least five (5) pounds of dry ice are used. Also, ship overnight express so that specimens will not arrive on a weekend or holiday. Address:

Daniel F. Hayes, M.D.
Lombardi Cancer Center
Room E504
Research Building
3970 Reservoir Road, NW
Washington, DC 20007
Telephone: 202-687-2103

8.4.3 Collection of whole blood for Genomic DNA studies:

Genomic DNA: Note: A separate portion of the consent form used for treatment studies must be signed for studies of genomic DNA.

One to two 8cc tubes of whole blood should be drawn in yellow topped tubes (Vacutainer #4606; acid-citrate dextrose solution). Two tubes are preferable. Collect and store tubes at ambient temperature (70°F, 25°C). Blood should **NOT** be refrigerated but should be stored in a cool place. Blood should be shippted within 24 hours of collection, at ambient temperature. Cold packs are not required. An original C-383 form must be submitted with each sample, with a copy of the form sent to the DMC. Ship to:

Daynice Skeen/Evangeline Reynolds/Lynn Dressler
UNC DNA Extraction Laboratory
University of North Carolina
CB #7304 Lineberger Cancer Research Center
112 MacNider Building
Chapel Hill, NC 27599-7304
Tel: 919-966-2620; Fax: 919-966-4244

Note: Blood samples should be sent by overnight carrier, Monday through Thursday. (For Thursday shipment, please send by priority overnight.) **DO NOT SHIP BLOOD ON FRIDAYS OR THE DAY BEFORE A HOLIDAY.**

If it is absolutely necessary to draw blood on a Friday or the day before a holiday, keep the blood at ambient temperature. Blood should be shipped within 72 hours. Therefore, blood drawn on a Friday should be shipped on Monday by overnight carrier for Tuesday delivery.

The UNC DNA Extraction Laboratory will perform leukocyte separation and DNA extraction. Lymphocyte DNA will be prepared using the ABI DNA extractor and the DNA stored at -70°C. The methods to be employed are those already in place for studies of ras mutations in leukemic cells by the CALGB.

8.5 **Shipment billing:** A Federal Express account has been established for this study. This account number should be used exclusively for shipment of specimens as detailed above. The Federal Express account number may be obtained by contacting the the CALGB Central Office at 773-702-9171.

8.6 **Self-Administered Family History of Cancer Questionnaire:** After the patient gives informed consent and is registered to CALGB 9484, the patient will be given a self administered questionnaire covering the above topic. The questionnaire requires a short time to complete and should be submitted within 2 weeks of entry onto CALGB 9484. The institutional data managers should use the self-addressed envelope to send the completed questionnaires to:

CALGB Data Management Center
2200 West Main Street, Suite 430
Durham, NC 27705
Phone: 919-286-0045
Fax: 919-286-1142

The CALGB DMC will forward a copy of the questionnaires to the Specialized Registry staff at the Epidemiology Office of the University of North Carolina.

A sub-sample of patients identified on the basis of information provided by the self-administered questionnaire (CALGB Family History of Cancer Questionnaire) will be contacted by the epidemiology office staff at the University of North Carolina, Chapel Hill, and asked to complete a more extensive phone interview (CALGB Detailed Family History and Exposure Telephone Interview). The participating epidemiology staff is funded by a grant, so the phone interviews will be conducted at no charge to patients or their families. Prior to contacting patients by phone, the epidemiology staff will contact the institution that registered the patient to assure that the patient is still alive and not hospitalized, in order to minimize stress to the patient and/or family.

8.7 **Receipt of Specimens:** A system is being implemented so that Centers receiving specimens will electronically report to the CALGB database the receipt and condition of the specimen using standard CALGB procedures. However, until this system is fully operational, initiating Centers will e-mail or fax this information to the responsible data coordinator at the Data Management Center.

8.8 Tracking of Patient Specimen Submission: The CALGB data management system (or data coordinator, until the system is fully implemented) will track patients who are entered on this CALGB protocol and generate reminders to institutions that have entered patients on this protocol if the specimens are not received at the appropriate office or lab in a timely manner.

8.9 Training of data managers: On a regular basis, not less than once a year, a portion of the CALGB Clinical Research Associates workshop will be devoted to instruction of the proper methods of obtaining and shipping the above specimens.

8.10 Specialized Registry Policies: Application for use of Registry. Use of the registry is under the supervision of the Specialized Registry Steering Committee appointed by Dr. O. Ross McIntyre, M.D. the Principal Investigator on the grant from the U.S. Army Medical Research and Materiel Command which supports the registry. Charter members of the Steering Committee are listed below:

Name	CALGB position	Institution
O. Ross McIntyre, M.D.	Chairman.	Dartmouth Medical School
Robert Millikan, DVM, Ph.D	Co-PI	U. North Carolina
Maurice Barcos, M.D.	Pathology	Roswell Park
Donald Berry, Ph.D.	Statistician	Duke Univ.
Larry Norton, M.D.	Br. Com. Chm	Memorial Sloan-Kettering
Lauren Schnaper, M.D.	Surgery	U. Maryland
Edison Liu, M.D.	Chm. Cor. Sci.	U. North Carolina
Dale Sandler, Ph.D.	Chm. Epi. Com	NIEHS
Daniel Hayes, M.D.	Vice Chm. Br. Com.	Dana Farber
Judy Garber, M.D.	Member, Cor Sci	Dana Farber
Alice Kornblith, Ph.D.	Member, Psy Onc	Memorial Sloan-Kettering
Deborah Collyar	Patient Advocate	
Sue Moore	Patient Advocate	

Additional members may be appointed to the steering committee from time to time and will be noted in revisions to this protocol. However, it is anticipated that there will be minimal turnover of steering committee membership.

Laboratory and epidemiological studies that are approved by the Steering Committee for the use of the Specialized Registry will be kept on file at the CALGB Central Office and incorporated into this appendix. Each project will have received IRB approval at the submitting investigator's institution. Individual projects will not require IRB approval at individual CALGB institutions.

Procedures for Project Approval/Appendix Inclusion: Investigators wishing to use the resources of the registry must apply to the Steering Committee for permission to obtain materials or information from the registry. In each case the investigator must submit a protocol for the proposed study and furnish evidence that it has been reviewed and approved by the Institutional Review Board at the investigator's institution. In addition, the investigator must accept other conditions governing the collaboration. If the investigator is a member of CALGB, usual policies governing Group data management and publication will prevail. If the user is not a member of CALGB, a CALGB co-chair of the proposed study will be appointed by the Steering Committee in consultation with the investigator. The person serving as co-chair will assist in trouble-shooting and will present a synopsis of the status of the study at CALGB meetings, if the non-CALGB investigator is unable to attend. The investigator will be asked to sign a letter outlining the essential features of the collaboration with the Specialized Registry. An important feature of the collaboration is that the investigator will furnish results to the CALGB Data Management Center where analyses will be performed by the CALGB statistician. No information concerning the patient, other than the specimen from an individual on a CALGB trial, will be furnished to the investigator. In this manner the laboratory will remain blinded as to

the other information available about the patient and patient confidentiality will be protected as well. The letter stipulates that the investigator will not provide specimens received from the registry to third parties. These procedures have been put in place in order to: protect patient confidentiality; blind the laboratory doing tests with respect to patient outcomes until the laboratory has submitted its results and the responsible CALGB statistician has performed an analysis; and achieve agreement on the presentation and publication of results prior to commencing with the work.

It is anticipated that the Specialized Registry will be used by a large number of investigators. This protocol will not be amended to describe the details of each laboratory or other use to which an approved investigator may put the Registry, however, as stated above each project using the Registry will have received IRB approval at the investigator's institution. It is anticipated that methodologies in the laboratories will be rapidly evolving during the lifetime of the Registry and that a number of hypotheses will be offered in the future that could not be conceived today. The patients have been given assurance that the Registry will approve studies that are limited to those involving cancer, and it is not intended to reconsent the patient for each new test for which the registry will be used.

Studies of heritable cancer genes will be conducted according to CALGB policies for the studies of such genes.

9.0 REFERENCES

1. Rothman K. Modern Epidemiology, pp 95-96, Little Brown, Boston, 1986.

2. Khoury M, James L. Population and familial relative risks of disease associated with environmental factors in the presence of gene-environment interactions. Am. J Epidemiol. 137:1241-50, 1993.

3. Charrow RP. Bench Notes- Judgements: Whose Tissue is it, Anyway? Jr. NIH Research, 6: 79-81, 1994

4. Kaaks R, Tweel I, van Noord P, Riboli E. Efficient use of biological banks for biochemical epidemiology: exploratory hypothesis testing by means of a sequential t-test. Epidemiology 5: 429-38, 1994.

5. Begg C, Zhang Z. Statistical analysis of molecular epidemiology studies employing case-series. Cancer Epidemiology Biomarkers & Prevention 3: 173-75, 1994.

10.0 MODEL CONSENT CALGB 9484: LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

About Using Specimens and Interviews for Research

We would like to keep some of the left over tissue from your biopsy or surgery for future research. If you agree, this tissue will be sent to a repository where it will be preserved. Pieces of the tissue will be used in research to learn more about cancer. Precautions will be taken not to use up all of the cancer tissue in the specimen. If your institution ever needs the tissue again, the repository will return it in good condition within 24 hours.

The CALGB would also like to obtain some blood samples and urine samples from you. The blood sample will allow researchers to examine genes in cells that are not cancerous, and to look for substances in the plasma that may result from or contribute to the development of breast cancer. The urine samples may also be useful for similar purposes.

Because it is not possible for you or the CALGB to know what will be discovered in the future and what additional tests may be appropriate at that time, we ask that you give permission for such studies without being recontacted for permission for each test. The research that may be done with your tissue and blood or urine samples probably will not help you. It might help people who have cancer and other diseases in the future.

CALGB may also wish to contact you by phone in order to ask questions about things that may relate to the cause and prevention of breast cancer.

If you agree, we will use your blood cells for genetic research (about diseases that are passed on in families). If your specimens are used for this kind of research, the results will not be returned to your hospital or doctor or put in your health records. If you do not want your blood cells to be used for genetic research, you can still agree to have your tissue and urine used for other types of research that do not involve diseases that are passed on in families.

The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue or to furnish the blood and urine specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that we can have the specimens and you decide to change your mind later, just contact us and let us know that you do not want us to use your specimens. Then they will no longer be used for research

When tests have been completed with the specimens you have decided to let us have, the results may be combined with other information about you. Test results and information about you and your treatment are maintained in a confidential file in the CALGB computer. Only the responsible person at the CALGB database is able to combine the results of tests on your tissue, blood or urine with other information about you, for instance, how well you respond to treatment. We will not reveal your name or other identifying information about you and your illness to researchers who perform the testing or anyone else. The CALGB has obtained a Certificate of Confidentiality from the U.S. Department of Health and Human Services that will also help to protect this information.

Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

Benefits

The benefits of research using the specimens include learning more about what causes cancer, and how to prevent, treat, and cure it.

Risks

There are very few risks to you. The risk of giving the blood sample when blood is being collected for tests required to manage your care is minimal as is the collection of the urine sample. The greatest risk is the release of information about you. The CALGB will protect your records so that your name, address, and phone number will be kept private. The chance that this information will be discovered by someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." No matter what you decide to do, it will not affect your care. If you have any questions, please talk to your doctor or nurse, or call the Institutional Review Board (IRB) representative (phone number given below).

1. My tissue may be kept for use in research to learn about, prevent, treat, or cure cancer.

   Yes No

2. An interviewer from CALGB may contact me by phone to ask questions that relate to the cause, prevention and treatment of breast cancer.

   Yes No

3. I also give my permission to be contacted by phone in the future if it might assist in this kind of research.

   Yes No

4. I give permission for blood samples to be obtained that will be used for tests of cancer genes that may run in families. I understand that the results of this type of test will remain confidential in the CALGB computer file and will not be returned to me, my hospital or my doctor.

   Yes No

5. I give my permission for urine and plasma (blood) samples to be obtained for tests relating to cancer.

   Yes No

(Patient's Signature)	(Date)
(Physician's Signature)	(Date)
(Name of Responsible Investigator)	(Phone #)
(Name of IRB Representative)	(Phone #)

APPENDIX I

Data Collection Forms

C-350 CALGB Pathology Routing Form

C-383 CALGB Specimen Routing Form: Whole Blood

C-384 CALGB Specimen Routing Form: Plasma

INSTRUCTIONS FOR
CALGB: TRACKING FORM (TISSUE BLOCKS)
NO. C-490

A. PURPOSE

To track sample submission and receipt of information for tissue blocks submitted as part of the protocol.

B. FORM SPECIFIC INSTRUCTIONS

1. If the data on this form are amendments to previously submitted data, indicate this by checking "YES" in the box in the upper right corner of the form; otherwise leave this space blank. Highlight and circle all amended data.

2. Record patient's name, hospital number and main member institution/adjunct information for all patients. Only complete the participating group information if you are a member of a group other than CALGB.

3. When completing "specify" fields try to limit comment wording to 20 or fewer characters for computer data entry. A more complete explanation may be provided underneath the field or with an addendum.

4. The SUBMITTING INSTITUTION must indicate if the sample has been sent along with the form. Complete the information in the box on the LEFT as indicated. Note that date sample collected refers to the date the tissue was removed from the patient. Path number is the pathology identification number or accession number used by the institution to identify this sample. Specify the date blocks were sent and the sender's name and phone number. The submitting institution should retain a copy of the form and submit a copy to the CALGB Data Management Center. The original should be included with the blocks.

5. NOTE: ALL BLOCKS SUBMITTED MUST BE ACCOMPANIED BY THIS FORM AND APPROPRIATE PATHOLOGY REPORT(S). See the Sample Submission section of the protocol for details.

6. The RECEIVING INSTITUTION must complete the information in the box on the RIGHT as indicated. Specify the date blocks were received and the receiver's name and phone number. A copy of this from should be kept for his/her records and the original should be sent to the CALGB Data Management Center, 2200 West Main Street, and Suite 340, Durham, North Carolina 27705.

CALGB Form:	C-490
CALGB Study No.:	______
CALGB Patient ID:	______
Amended Data?:	___ Yes

CALGB: TRACKING FORM (TISSUE BLOCKS)

INSTRUCTIONS: This form is to be completed and submitted as required by protocol. Information in the upper right box must be completed for this form to be accepted. Do not leave any entries black. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Retain a copy for your records and submit a copy to Data Management Center. Submit original with required samples and appropriate report(s) to the pathology coordinating office mentioned in the histology specimen submission section of your protocol.

Patient's Name ______________________

Patient Hospital number ______________________

Main Member Institution/Adjunct ______________________

Participating Group ______________________

Participating Group Protocol No. ______________________

Participating Group Patient No. ______________________

☐ **Does specimen accompany this form? (1-No, 2-Yes)**

If no, specify reason: ______________________

If yes, complete the remainder of this form.

☐ **Is this patient enrolled in a companion study? (1-No, 2-Yes)**

☐☐☐☐ **If yes, please give companion study number.**

TO BE COMPLETED BY SUBMITTING INSTITUTION

☐☐ ☐☐ ☐☐☐☐ Date Sample Collected
M D Y

☐☐ Sample extraction
(01-Biopsy, 18-Lumpectomy, 06-Mastectomy)

☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Pathology accession no.

☐☐ ☐☐ ☐☐☐☐
M D Y
Date blocks and pathology reports submitted

____
Submitted By

____
Phone No.

TO BE COMPLETED BY RECEIVING INSTITUTION

☐☐ ☐☐ ☐☐☐☐ Date Sample Received
M D Y

☐☐ Sample condition
1- ok 3-missing
2-damaged 11-poor fixation

☐ Pathology report received? (1-No, 2-Yes)

☐ Does block match path report? (1-No, 2-Yes)

____
Received By

____
Phone No.

INSTRUCTIONS FOR
CALGB SPECIMEN ROUTING FORM (C-383):
WHOLE BLOOD

A. Purpose: To provide identifying information that will accompany the tube(s) of whole blood.

B. Form Specific Instructions:

1. If any data on this form is an amendment to previously submitted data, indicate this by checking "Yes" in the box located in the upper right-hand corner of the form; otherwise, leave this space blank. Highlight and circle ALL amended data.

2. Record the patient's name, hospital number and main member institution/adjunct information. Only complete the participating group information if you are a member of a group other than CALGB (EGOC, SWOG, etc.).

3. Record the CALGB study number (the correlative science study number) in the box located in the upper right-hand corner of the form. Record the CALGB treatment study number in the section entitled "To be completed by submitting institution".

4. The SUBMITTING INSTITUTION must complete the information in the TOP PORTION of the form, as indicated. Do NOT add decimal points or boxes to any data on this form.

5. Record the month, day, and 4-digit year that the tube(s) of whole blood were collected from the patient.

6. Code whether the specimen will accompany this form to the sample collection site. If the specimen does NOT accompany this form, be sure to specify the reason.

7. Record the number of tubes of whole blood being submitted.

8 Record the month, day, and 4-digit year that the tube(s) of whole blood were sent.

9 Code whether the specimen collected is a pre-treatment sample, was collected during initial treatment, during follow-up (the patient is no longer receiving the protocol treatment) or at the time of relapse. Ship each specimen separately (e.g. pre-treatment specimen versus during treatment specimen versus follow-up specimen, etc.).

10 Upon completion of the top portion of the form, print or type your name and the date you completed the form. Make two copies of this form, keep one copy for your records and send the other copy to the CALGB Data Management Center. Submit the original form along with the sample to the appropriate CALGB laboratory, as specified by the protocol.

11 See the Sample Submission section of the protocol for PACKAGING and SHIPPING instructions.

12 The RECEIVING INSTITUTION must complete the MIDDLE PORTION of the form as indicated. Specify the date the sample was received and the name of the receiver. If the exact volume of aliquot is unknown, estimate the average volume. Return a copy of the entire form to the CALGB Data Management Center.

13. The section FOR DMC USE ONLY has been pre-coded. Do not edit this portion.

CALGB: SPECIMEN ROUTING FORM:
WHOLE BLOOD

CALGB Form:	C-383
CALGB Study No.:	_____
CALGB Patient ID.:	_____
Amended Data?:	_____ Yes

INSTRUCTIONS: The original of this form is to be completed and submitted along with required whole blood specimen. Information in the upper right box must be completed for this form to be accepted. Do not leave any entries blank. Circle and highlight all amended data. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Retain a copy of this form for your records and submit a copy to the CALGB Data Management Center. Submit the original form with the specimen to the appropriate CALGB Laboratory. SEE THE PROTOCOL FOR PACKAGING AND SHIPPING INSTRUCTIONS.

Patient's Name _____ Participating Group _____

Patient Hospital Number _____ Participating Group Protocol No. _____

Main Member Institution/Adjunct _____ Participating Group Patient No. _____

TO BE COMPLETED BY SUBMITTING INSTITUTION

[1] Blood Sample **(whole blood)** [ ][ ] [ ][ ] [ ][ ][ ][ ] Date whole blood specimen collected (M D Y)

[ ][ ][ ][ ][ ][ ] CALGB Treatment Study [ ] Does specimen accompany this form? (1-No, 2-Yes)

If ***no***, specify reason: _____

If ***yes***, complete the remainder of this form.

[ ][ ] Number of tubes submitted [ ][ ] [ ][ ] [ ][ ][ ][ ] Date sample sent (M D Y)

[ ][ ] Specimen Collected

02-Pre-treatment
21-During Initial Treatment
18-During Follow-up, No Therapy
14-At Relapse/Progression

Responsible treating physician: _____

Completed By: _____ **Date Completed:** ____/____/____
(Print or Type Name)

Phone Number to be used in event of sample problems: _____

TO BE COMPLETED BY RECEIVING INSTITUTION/LABORATORY

[ ][ ] Sample Condition [ ][ ] [ ][ ] [ ][ ][ ][ ] Date sample received (M D Y)

01-Okay
02-Damaged
03-Missing
07-Insufficient amount
16-Damaged but stored
17-Thawed but stored
19-Improperly stored

[ ][ ][ ][ ][ ][ ][ ][ ][ ] Sample ID no. [ ][ ] # of Aliquots [ ][ ][ ] Average aliquot volume (cc)

Sample received by _____

FOR DMC USE ONLY

[1] Specimen Type (1: peripheral blood)
[1] Blood Sample (1: whole blood)
[8] Method of Sample Collection (8: venous)
[6] Sample Container (6: yellow top vial)
[2] Class of Units (2: volume)
[1 5] Unit of Measure (15: cubic centimeter)
[1] Sample Storage (1: room temperature)

INSTRUCTIONS FOR
CALGB SPECIMEN ROUTING FORM (C-384):
PLASMA

A. Purpose: To provide identifying information that will accompany the tube(s) of plasma.

B. Form Specific Instructions:

1. If any data on this form is an amendment to previously submitted data, indicate this by checking "Yes" in the box located in the upper right-hand corner of the form; otherwise, leave this space blank. Highlight and circle ALL amended data.

2. Record the patient's name, hospital number and main member institution/adjunct information. Only complete the participating group information if you are a member of a group other than CALGB (EGOC, SWOG, etc.).

3. Record the CALGB study number (the correlative science study number) in the box located in the upper right-hand corner of the form. Record the CALGB treatment study number in the section entitled "To be completed by submitting institution".

4. The SUBMITTING INSTITUTION must complete the information in the TOP PORTION of the form, as indicated. Do NOT add decimal points or boxes to any data on this form.

5. Record the month, day, and 4-digit year that the tube(s) of plasma were **collected** from the patient.

6. Code whether the specimen will accompany this form to the sample collection site. If the specimen does NOT accompany this form, be sure to specify the reason.

7. Record the number of tubes of plasma being submitted.

8. Record the month, day, and 4-digit year that the tube(s) of plasma were **sent**.

9. Code whether the specimen collected is a pre-treatment sample, was collected during initial treatment, during follow-up (the patient is no longer receiving the protocol treatment) or at the time of relapse. Ship each specimen separately (e.g. pre-treatment specimen versus during treatment specimen versus follow-up specimen, etc.).

10 Upon completion of the top portion of the form, print or type your name and the date you completed the form. Make two copies of this form, keep one copy for your records and send the other copy to the CALGB Data Management Center. Submit the original form along with the sample to the appropriate CALGB laboratory, as specified by the protocol.

11. See the Sample Submission section of the protocol for PACKAGING and SHIPPING instructions.

12. The RECEIVING INSTITUTION must complete the MIDDLE PORTION of the form as indicated. Specify the date the sample was received and the name of the receiver. If the exact volume of aliquot is unknown, estimate the average volume. Return a copy of the entire form to the CALGB Data Management Center.

13. The section FOR DMC USE ONLY has been pre-coded. Do not edit this portion.

CALGB: SPECIMEN ROUTING FORM
PLASMA

CALGB Form:	C-384
CALGB Study No.:	_____
CALGB Patient ID.:	_____
Amended Data?:	_____ Yes

INSTRUCTIONS: The original of this form is to be completed and submitted along with required plasma specimen. Information in the upper right box must be completed for this form to be accepted. Do not leave any entries blank. Circle and highlight all amended data. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Retain a copy of this form for your records and submit a copy to the CALGB Data Management Center. Submit the original form with the specimen to the appropriate CALGB laboratory. SEE THE PROTOCOL FOR PACKAGING AND SHIPPING INSTRUCTIONS.

Patient's Name _____ Participating Group _____

Patient Hospital Number _____ Participating Group Protocol No. _____

Main Member Institution/Adjunct _____ Participating Group Patient No. _____

TO BE COMPLETED BY SUBMITTING INSTITUTION

[4] Blood Sample **(plasma)**

[ ][ ] [ ][ ] [ ][ ][ ][ ] Date plasma specimen collected
M D Y

[ ][ ][ ][ ][ ][ ] CALGB Treatment Study

[ ] Does specimen accompany this form? (1-No, 2-Yes)

If *no*, specify reason: _____

If *yes*, complete the remainder of this form.

[ ][ ] Number of tubes submitted

[ ][ ] [ ][ ] [ ][ ][ ][ ] Date sample sent
M D Y

[ ][ ] Specimen Collected
02-Pre-treatment
21-During Initial Treatment
18-During Follow-up, No Therapy
14-At Relapse/Progression

Responsible treating physician: _____

Completed By: _____ **Date Completed:** ____/____/____
(Print or Type Name)

Phone Number to be used in event of sample problems: _____

TO BE COMPLETED BY RECEIVING INSTITUTION/LABORATORY

[ ] Sample Condition
01-Okay
02-Damaged
03-Missing
07-Insufficient amount
16-Damaged but stored
17-Thawed but stored
19-Improperly stored

[ ][ ] [ ][ ] [ ][ ][ ][ ] Date sample received
M D Y

[ ][ ][ ][ ][ ][ ][ ][ ][ ] Sample ID no.

[ ][ ] # of Aliquots

[ ][ ][ ] Average aliquot volume (cc)

Sample received by _____

FOR DMC USE ONLY

[1] Specimen Type (1: peripheral blood)

[4] Blood Sample (4: plasma)

[8] Method of Sample Collection (8: venous)

[4] Sample Container (4: purple top vial)

[2] Class of Units (2: volume)

[1][5] Unit of Measure (15: cubic centimeter)

[7] Sample Storage (7: -20 degrees C)

INSTRUCTIONS FOR
CALGB URINE SAMPLE TRACKING FORM
NO. C-449

A. Purpose

To track sample submission and receipt information for urine samples submitted as part of the protocol. This form is to be submitted as required by protocol.

B. Form Specific Instructions

1. If any data on this form is an amendment to previously submitted data, indicate this by checking "Yes" in the box located in the upper right-hand corner of the form; otherwise, leave this space blank. Highlight and circle ALL amended data.

2. Record the patient's name, hospital number and main member institution/adjunct information. Only complete the participating group information if you are a member of a group other than CALGB (ECOG, SWOG, etc.).

3. Record the CALGB study number (the correlative science study number) in the box located in the upper right-hand corner of the form. Record the CALGB treatment study number in the section entitled "To be completed by submitting institution".

4. The SUMBITTING INSTITUTION must complete the information in the TOP PORTION of the form, as indicated. Note that the "date sample collected" refers to the date the sample was collected from the patient. Also specify the date the sample was sent and the responsible treating physician's name. Time should be recorded using military clock (i.e., a 24-hour clock). If the exact time of sample collection is unknown, fill in a reasonable estimate of time. If the exact volume of the sample is unknown, an estimated volume is acceptable. Do NOT add decimal points or boxes to any data on this form.

5. Upon completion of the top portion of the form, print or type **your name** and the date you completed the form. Make two copies of this form, keep one copy for your records and send the other copy to the CALGB Data Management Center. Submit the original form along with the sample to the appropriate CALGB laboratory, as specified by the protocol.

6. See the Sample Submission section of the protocol for PACKAGING and SHIPPING instructions.

7. The RECEIVING INSTITUTION must complete the MIDDLE PORTION of the form as indicated. Specify the date the sample was received and the name of the receiver. If the exact volume of aliquot is unknown, estimate the average volume. Return a copy of the entire form to the CALGB Data Management Center.

8. The section FOR DMC USE ONLY has been pre-coded. Do not edit this portion.

CALGB: URINE SAMPLE TRACKING FORM

INSTRUCTIONS: This form is to be completed and submitted as required by protocol. Information in the upper right box must be completed for this form to be accepted. Do not leave any entries blank. Enter -1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Retain a copy of this form for your records and submit a copy to the CALGB Data Management Center. Submit the original form with the sample to the appropriate CALGB laboratory. SEE THE PROTOCOL FOR PACKAGING AND SHIPPING INSTRUCTIONS.

CALGB Form: C-449
CALGB Study No.: _____
CALGB Patient ID.: _____
Amended Data?: _____ Yes

Patient's Name _____ Participating Group _____

Patient Hospital Number _____ Participating Group Protocol No. _____

Main Member Institution/Adjunct _____ Participating Group Patient No. _____

TO BE COMPLETED BY SUBMITTING INSTITUTION

[ ][ ] [ ][ ] [ ][ ][ ][ ] Date sample collected
M D Y

[ ][ ] Specimen Collected
02-Pre-treatment
21-During Initial Treatment
18-During Follow-up, No Therapy
14-At Relapse/Progression

[ ][ ][ ][ ][ ][ ] CALGB Treatment Study

[ ][ ] : [ ][ ] Time sample collected (h:m 24 hour clock)

[ ][ ][ ] Approximate Volume of sample (ml)

[ ][ ] [ ][ ] [ ][ ][ ][ ] Date sample sent
M D Y

NOTE: ALL URINE SAMPLES SHOULD BE STORED AND SHIPPED AT A TEMPERATURE OF -20 DEGREES CELSIUS.

Responsible treating physician: _____

Completed By: _____ **Date Completed:** ____/____/____
(Print or Type Name)

Phone Number to be used in event of sample problems: _____

TO BE COMPLETED BY RECEIVING INSTITUTION/LABORATORY

[ ][ ] Sample Condition
1-O.K
2-Damaged
3-Missing
7-Insufficient amount
16-Damaged but stored
17-Thawed but stored
19-Improperly stored

[ ][ ] [ ][ ] [ ][ ][ ][ ] Date sample received
M D Y

[ ][ ][ ][ ][ ][ ][ ][ ][ ] Sample ID no

[ ][ ] # of Aliquots

[ ][ ][ ] Average aliquot volume (ml)

Received by _____

FOR DMC USE ONLY

[1][1] Specimen Type (11: urine)

[1][4] Method of Sample Collection (14: urination)

[2][0] Sample Container (20: plastic freezing tube)

[2] Class of Units (2: volume)

[1][2] Unit of Measure (12: millimeter)

[7] Sample Storage (7: -20 degrees C)

The questionnaires that accompany this protocol have been included in this progress report appendix as items 1 and 2.

APPENDIX III

CALGB Policy Governing Genetic Studies

CALGB POLICIES GOVERNING GENETIC STUDIES

Whereas studies of somatic mutations in cancer cells pose little risk to the patient, studies of heritable cancer genes may lead to discrimination by insurers and employers. In addition, the discovery of a familial cancer gene carries with it psycho-social consequences which are only imperfectly understood at present and which add to the above risk. For this reason, all consents for studies of heritable cancer genes must be obtained prospectively. These consents should provide adequate information to allow the patient to assess the risk of participation in the study, and should indicate the steps that CALGB is taking to reduce such risks.

Banked material, already obtained from patients on CALGB protocols may be used for studies of heritable genes, but in this case, a reconsent must be obtained from the patient.

The CALGB will take steps to secure, if possible, a Certificate of Confidentiality from the NIH in order to reduce the risk that disclosure of patient identifiers along with information about gene studies will occur.

CALGB will ask its investigators to advocate the passage of state laws preventing insurers and employers from asking for any information about whether the person has had a diagnosis of cancer or whether the person or family members have been the subject of genetic testing.

Because it is unknown what tests may be appropriate on specimens during the time the specimen is banked, the patient will be asked to grant a broad permission for testing. The patient will be informed that heritable gene studies will be limited to those relevant to cancer. The patient will not be asked to grant permission for each individual laboratory study to be performed. Instead, the patient will be assured that all laboratory investigators will have had their project approved by their respective institutional review board prior to receiving permission to study their tissue.

Access to the tissue bank will be granted upon the recommendation of the appropriate committee overseeing the bank. Each investigator using the bank will provide a written description of the project for which the bank is to be used and will be limited to that project. The investigators must agree that all data resulting from their studies will be furnished to the Data Management Center for entry into the CALGB data base. This agreement will also contain provisions for maintaining patient confidentiality. Clinical information from the CALGB data base will not be provided to users of the bank, except in reports prepared by the CALGB which will lack patient identifiers.

Each protocol describing studies of heritable cancer genes will define optimal patient support and set minimum limits for the level of genetic counseling that must be in place in each institution to allow protocol activation.
The CALGB will establish a committee responsible for review of studies involving heritable cancer genes. The charge to this committee is to consider the short and long-term risks associated with protocols involving studies of heritable genes and to advise the Chair with respect to the appropriate actions concerning these studies. The committee is also responsible for reviewing the resources available for genetic counseling at CALGB member institutions and approving these programs as a requisite for institutional participation in designated protocols. This committee will be comprised of CALGB members as well as representatives of the public.

APPENDIX IV

DHHS Confidentiality Certificate

DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

Washington, D.C. 20201

JUN 24 1996

Karen Sartell, M.A.
Cancer and Leukemia Group B
Central Office of the Chairman
208 South LaSalle Street, Suite 2000
Chicago, IL 60604-1104

Dear Ms. Sartell:

I am happy to send you the certificate of confidentiality for the research project "Cancer and Leukemia Group B -- Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry."

Please be sure that the informational statement given to participants accurately states the intended uses of personally-identifiable information and the confidentiality protections, including the protection provided by the certificate of confidentiality, with its limitations and exceptions.

May I ask that you advise me of any situation in which the certificate is employed to resist disclosure of information in legal proceedings. I am at 440D Humphrey Building, telephone (202) 690-5896 (direct dial, sometimes answered by machine) or (202) 690-7100, telefax (202) 690-5882. Internet: jfanning@osaspe.dhhs.gov.

If attorneys for the University wish to discuss the use of the certificate, they may contact the Chief Counsel of the Public Health Service, Mr. Richard Riseberg, at (301) 443-2644.

If you have any questions, or if we can otherwise help, please call.

Sincerely yours,

John P. Fanning
Senior Policy Analyst
Division of Data Policy
Office of Program Systems

CONFIDENTIALITY CERTIFICATE

issued to

Employees of

Cancer and Leukemia Group B
and All Participating Institutions

and Other Participants

conducting research known as

LINKAGE OF MOLECULAR AND EPIDEMIOLOGICAL BREAST CANCER INVESTIGATIONS WITH TREATMENT DATA: A SPECIALIZED REGISTRY

In accordance with the provisions of section 301(d) of the Public Health Service Act (42 U.S.C. § 241(d)) this certificate is issued to protect the privacy of research subjects by withholding their identities from all persons not connected with the research.

Under authority vested in the Secretary of Health and Human Services under that section, all persons who --

(1) are employed by Cancer and Leukemia Group B, and all participating institutions, and their contractors and cooperating agencies; and

(2) have, in the course of that employment, access to the information which would identify individuals who are the subjects of a research project entitled "Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry"

are hereby authorized to protect the privacy of the individuals who are the subjects of that research by withholding their names and other identifying characteristics from all persons not connected with the conduct of that research, with the exceptions and limitations set forth below.

The purpose of this research project is to collect breast tissue, plasma and urine from cancer patients; review and confirm the histopathological diagnosis of breast cancer on submitted tissue; gather key family, endocrine and reproductive history, and exposure data, on subjects; and provide specimens to approved investigators for study, and receive results of these studies.

As provided in section 301(d) of the Public Health Service Act (42 U.S.C. § 241(d)),

> "Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals."

The following conditions apply to the protection provided under this certificate:

(1) This certificate does not authorize the Cancer and Leukemia Group B, participating institutions, or their contractors or cooperating agencies to refuse to reveal identifying information concerning research subjects if any of the following conditions exist:

(a) The subject (or, if he or she is legally incompetent, his or her guardian) consents in writing to disclosure of identifying information.

(b) Authorized personnel of the United States Department of Health and Human Services or of the U.S. Army Medical Research and Materiel Command request such information for audit or program evaluation of the research project, or for investigation of the Cancer and Leukemia Group B, participating institutions, or their contractors or employees in carrying out the research project.

(c) Release is required by the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §§ 301 et seq.) or regulations promulgated thereunder (Title 21, Code of Federal Regulations).

(2) This certificate requires that there be no disclosures of identifying characteristics of research subjects in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings to compel disclosure of the identifying characteristics of research subjects, except as provided for in paragraph (1), above.

(3) The confidentiality certificate does not govern the voluntary disclosure of identifying characteristics of research subjects.

(4) This certificate does not represent an endorsement of the research project by the Department of Health and Human Services.

(5) All research subjects in the project will be given a fair, clear explanation of the protection this certificate affords, and of the limitations and exceptions to the protection.

(6) This certificate is effective upon issuance, and will expire at the end of June 2011 or sooner if the holder is notified of cancellation in accordance with the procedures set out in 42 C.F.R. § 2a.8. The protection afforded by this certificate of confidentiality is permanent (including after death) for persons who participated as subjects in the research during any time the certificate was in effect.

Date: JUN 19 1996

Philip R. Lee, M.D.
Assistant Secretary for Health

APPENDIX 8. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES EMPLOYED BY CALGB PATHOLOGY OFFICE. APPROVAL FROM THE SOLID TUMOR CORRELATIVE SCIENCE COMMITTEE AND CENTRAL TISSUE BANK COMMITTEE.

Pathology policy development for tissue banking:

Although tissue acquisition for this study commenced October, 1995, the Pathology Coordinating Office has had prior experience collecting blocks as a mandatory requirement for four breast cancer clinical trials now active in the CALGB. Because of varying certification and licensing requirements placed at the federal, state and professional society level concerning retention of blocks by institutional surgical pathology laboratories it is not always clear whether all or simply representative tissue blocks are required to remain on file by a pathology laboratory. Some hospital policies prohibit release of an entire block for storage, but will allow cut sections to be stored. Many hospitals are willing to release blocks if they can be assured of accessibility to representative material for any future medical-legal need. In order to address these concerns, and offer alternatives for those hospitals whose policies prohibit release of an entire block for storage, we have developed a Tissue Bank policy for this study.

Quality control and quality assurance of tissue blocks/sections:

Several precautions are taken to ensure that appropriate processing is performed to accommodate a variety of laboratory uses. High quality sections that are representative of the histopathologic diagnosis of breast cancer are required. For example, to reduce possible DNA contamination for molecular assays the following precautions are taken: gloves are worn by the histotechnician, the disposable blade is wiped down with 10% bleach, followed by 70% alcohol between each block unless a new blade is used; the water bath surface is cleaned between each block, clean forceps are used for each block. In addition, all thick, 10 micron sections cut for molecular assays are placed on uncoated slides (to facilitate scraping) and are stored at 4 degrees. All intact blocks are stored at 4 degrees to minimize antigen deterioration. Thin sections cut for immunohistochemistry are stored at a minimum of 4 degrees (preferably -70°C) and are placed on coated slides (to avoid tissue detachment during assay). H & E sections are cut at different levels throughout the block to ensure that representative tissue is being used for a particular assay. These procedures also address the steps to be taken when minimal tissue is available from the block. This ensures that tissue will not be exhausted in these blocks.

OUTLINE OF PROCEDURES

PATHOLOGY QUALITY CONTROL AND QUALITY ASSURANCE

Procedure for Cutting Sections for the Linked Registry:

I. Quality assurance:

A. Histotech should wear gloves to prevent DNA contamination

B. Disposable blade should be changed between each block
or
Wipe down blade with 10% bleach, followed by 70% alcohol between each block

C. Clean water bath surface between each block to prevent contamination

D. Clean forceps or other instruments used for separating ribbon between each block

E. All 10 micron sections should be placed on uncoated slides and stored at room temp.

F. All 4 micron sections should be placed on superfrost+ coated slides.*

1. H & E sections should be stored at room temperature

2. All other 4 microns sections should be stored in a slide box at 4 degrees.

G. Do not place any cut sections on the slide warmer tray.

II. Sequence of sectioning:

Overall:

top H & E section-coated slide

20, 4 micron sections-coated slide (IHC)

middle H & E (a) section- coated slide

10, 10 micron sections-uncoated slides (Molecular)

middle H & E (b) section - coated slide

3, 50 micron sections- in screw-top glass tubes (Flow Cytometry)

bottom H & E section- coated slide

Labeling:

label all sections with specific pathology block number

label all sections with clinical protocol number and patient protocol

number; indicate group (ECOG, SWOG, CALGB, etc.)

number serial sections (1-20 for 4 micron; 1-10 for 10 micron)

indicate date that sections were cut: "cut date 00/00/00"

top H & E section: label "top"

middle H & E sections: ;label "middle a"; " middle b"

bottom H & E section: label "bottom"

A. Optimal sequence:

1. Cut 1, 4 micron section on coated slide-place in wire rack for H & E staining. (label "top")

2. Cut 20, 4 micron sections on coated slides-place in slide box, store at 4 degrees.

3. Cut 1, 4 micron section on coated slide-place in wire rack for H & E staining (label "middle" a)

4. Cut, 10, 10 micron sections on uncoated slides-place in separate slide box and store at room temperature.

5. Cut 1, 4 micron section on coated slide-place in wire rack for H & E staining (label "middle b")

6. Cut, 3, 50micron sections, place curled sections in a screw top glass tube

7. Cut 1, 4 micron section on coated slide-place in wire rack for H & E staining (label "bottom")

B. When minimal tissue is available: omit the 50 micron sections for flow cytometry first, then if there is still insufficient tissue to cut the 20 4micron sections for IHC and 10, 10micron sections for molecular; follow the following procedures (each level indicates less tissue available for cutting):

Level I.: (10, 4u;5,10u)

1. Cut top H & E section (coated slide).

2. Cut 10,4 micron sections (coated slide)

3. Cut middle H & E section (coated slide)

4. Cut 5, 10 micron sections (uncoated slide)

5. Cut bottom H & E section (coated slide)

Level II:(5,4u; 3, 10u)

1. Cut top H & E section (coated slide)

2. Cut 5,4 micron sections (coated slide)

3. Cut middle H & E section (coated slide)

4. Cut 3, 10 micron sections (uncoated slide)

5. Cut bottom H & E (coated slide)

Level III: (10 ,4 u sections; 5 on coated slides, 5 on uncoated slides)

1. Cut top H & E section (coated slide)

2. Cut 5, 4micron sections (coated slide)

3. Cut 5, 4 micron sections (uncoated slides)

4. Cut bottom H & E section (coated slide)

Note: 5 sections on uncoated slides; no middle H & E needed.

TISSUE BANKING POLICY FOR PARAFFIN BLOCKS IN THE LINKED TUMOR REGISTRY:

General Policy:

1. All precautions are taken to prevent exhausting tissue on the block.

2. A minimum of three H & E sections (obtained at different thicknesses) will remain on file at the CALGB Pathology office and are available to the submitting institution if needed.
3. A minimum of 2 unstained sections will remain on file and will be available to the submitting institution if needed.
4. Whenever there is an immediate medical or legal need, the unused tissue, along with an H & E section will be returned by overnight mail to the submitting institution.

Standard Tissue Processing:

It is optimal to obtain and bank the entire tissue block so that tissue can be sectioned freshly as needed, as certain antigens (e.g. p53) and other components deteriorate over time when tissue is pre-cut and stored as thin sections. Since it is impossible to predict the effect that extended storage might have on the detection of future markers, a consensus was reached at a recent NCI Inter group Tissue Banking meeting, that tissues be ideally sectioned freshly as needed for biologic makers. Blocks that are submitted to the CALGB pathology office are maintained in a secure space and appropriately recorded into our database. The CALGB is expending significant resources to establish and maintain a tissue surveillance database, expand physical storage capacity and optimize storage conditions for optimal monitoring and quality control for processing, storage and utilization of these tissues. Utilization of tissues occurs only after the proposed scientific study has received approval from the Steering Committee and Solid Tumor Correlative Science committees. Blocks are sectioned freshly for the appropriate assay and are processed in different ways and with special precautions: e.g.. for immunohistochemical studies, 4micron sections on coated slides are prepared and maintained at 4 degrees or colder (-70 degrees is preferable); for DNA extraction studies, 10 micron sections on uncoated slides are prepared carefully to prevent DNA contamination (stored at 4 degrees) and for flow cytometric studies, 3, 50 micron sections are prepared (stored at 4 degrees), in which tumor rich areas are separated from tumor poor areas.

Expedited Tissue Processing:

Although it is optimal to bank blocks so that tissue can be sectioned freshly as needed, we realize that various situations may preclude institutional block submission for banking purposes (institutional policies, legal requirements, minimal embedded tissue). If , for these reasons, a block cannot be maintained in the CALGB Tissue Bank, we ask you to consider submitting the corresponding block for a period of 2-8 weeks, during which time the CALGB pathology office will expedite tissue processing according to the above guidelines, store the sections at 4 degrees or colder (-70 degrees is preferable) for utilization in companion trials (that do not incorporate labile antigens) and return the blocks to your laboratory.

Institutional Tissue Processing:

> Because this material is of great importance for the conduct of CALGB Correlative Science studies and the future direction of our treatment protocols, we would also ask those institutions whose policies prohibit the release of any block from their institution to consider cutting the sections at their own institution. A detailed procedure for sectioning of the specimens can be sent to your laboratory. If needed, we will cover the cost of shipment of the cut sections to the CALGB pathology office. However, as detailed above, sectioning requires special dedication and precautions to prevent cross-contamination from a histotechnician and you may want to reconsider release of the block(s) for a 5 day turn around during which we will expedite the tissue sectioning from these cases.

APPENDIX **9. GUIDELINES RECENTLY APPROVED BY THE INTERGROUP SPECIMEN BANKING COMMITTEE TO STANDARDIZE THE FUNCTION AND OPERATION OF PATHOLOGY COORDINATING OFFICES AMONGST COOPERATIVE GROUPS.**

It will be noted that these guidelines conform to principles and procedures developed as part of the Linked Registry experience.

Safeguards to address medical/legal concerns of submitting pathologists:

- **For paraffin block specimens:**

A. ALL PRECAUTIONS TAKEN TO PREVENT EXHAUSTING TISSUE
   b. A minimum of 2, H & E sections (first and last) prepared and kept on file at PCO
   c. A minimum of 2, unstained thin sections (known to contain representative tissue) are archived and stored at 4 degrees at PCO and not distributed for assay
   d. H & E and archived sections and remaining tissue in block are kept on file at PCO and available to submitting institution by overnight carrier for any emergent medical or legal need
   e. Sections, not blocks are distributed to investigators

1. **Protection of patient privacy and confidentiality:**

- Unique identifier or code assigned to each specimen by respective PCO
- Specimens distributed to investigators are identified with this unique code
- No patient identifying information is distributed to a research investigator
- If pathology report is required by the investigator, patient identifying information (name, pathology number) must be omitted/whited out by PCO before distribution to investigator
- A mechanism must be in place to accommodate patient/participant request to withdraw their sample from a bank (e.g. samples will be disposed of appropriately-either destroyed (blood, plasma, DNA, RNA or in the case of paraffin blocks, returned to the submitting institution).
- A mechanism must be in place for restricted access to link id number and clinical information by informatics, statistical or data management personnel; investigators do not have access to this link
- For studies involving germline DNA (DNA extracted from blood or other normal cells) a separate informed must be obtained from the participant
- For studies involving germline DNA, (DNA extracted from blood or other normal cells) a certificate of confidentiality should be obtained
- (? Certificate of confidentiality for the banking activity)

2. Quality control of sectioning/storage/handling of specimens:

- Separate general guidelines should be developed for each type of specimen to address deterioration of proteins/nucleic acids; cross contamination of nucleic acid and applications
- formalin fixed paraffin embedded (FFPE) tissue material
- frozen material
- blood components (plasma, serum, packed red blood cells)
- DNA extraction
- RNA extraction
- Other fluids (urine, bone marrow, ascites, effusions)

3. Quality Assurance for Representativeness of Banked Specimens:

- All specimens received at the PCO must be accompanied by a specimen form to verify the identity of the specimen
- For paraffin blocks, any block received at PCO must be accompanied by corresponding pathology report, to verify identify and representativeness of block
- Pathology review of QA slide required prior to specimen distribution (H & E, touch preps)
- Paraffin blocks require H & E
- Frozen tissue requires touch prep/ H & E/Diffqwik
- QA results should be documented in database
- For paraffin blocks associated with an approved study, a minimum of 2, H & E sections (first and last) and optimally 3, H & E sections prepared at different depths (first, middle, last) and reviewed by pathologist to verify which cut sections are appropriate for distribution
- For paraffin blocks banked, without an approved study, no sectioning or H & E staining is performed until correlative science study is approved and active.
- If submitting institution requests return of block prior to study approval, sections should be taken as per standard cutting regimen
- QA slides remain on file at the respective PCO
- QA slides should not be distributed to any investigator; if needed, additional H & E slides can be cut for distribution to investigator

4. Scientific Review for Utilization of Specimens:

- Formal process of review by Intergroup Correlative Sciences Committee (unique science that requires population of cooperative groups to address hypothesis, ethics and integrity of proposal, preliminary results, investigator compliance with Intergroup policy, etc)
- Review by Intergroup Banking Committee for use of banked resources (e.g. for retrospective studies: adequacy of banked specimens for specific proposal-numbers, handling, processing, etc; for prospective studies: logistics, costs, technical aspects required for new prospective collection of material)
- No sample is distributed to any investigator without prior approval from Intergroup Correlative Sciences Committee and, when applicable, activation of protocol by respective cooperative group.

5. Policies for setting up a specimen bank:

- As a responsible guardian of Intergroup specimens, each bank will have safeguards in place to address medical-legal, confidentiality and privacy concerns of the patient, the submitting pathologist or other physician and the institution submitting the specimen

- Only Intergroup members can establish and maintain a bank for the Intergroup Banking Committee. If a non-Intergroup member wants to establish a bank for use, they must have an Intergroup member be a sponsor, and comply with Intergroup policy and procedures.
- All samples collected, processed, banked and distributed to investigators will be monitored in a database that follows the guidelines established by the Intergroup Informatics subcommittee.
- To protect patient confidentiality and privacy, distributed samples do not contain any identifiable patient information: only a unique specimen id number should be contained on the label of the distributed sample.
- Only select Intergroup personnel , not the investigator, will have the ability to match the sample number with clinical outcomes information

- Samples for Intergroup correlative science studies can only be obtained from patients who are registered to an Intergroup study (clinical trial or laboratory study).

6. Disclosure of research results:

- Individual results/data from any Intergroup correlative science study will NOT be disclosed to the patient/participant or physician. In this way, clinical /patient management decisions will not be made based on results from Intergroup Correlative Science studies
- Aggregate data, in the form of abstracts, manuscripts will be available for distribution upon request.
- Protocols that indicate disclosure of research results, must be approved by Intergroup Committee and policy will be defined on a protocol-by-protocol basis (e.g. appropriate informed consent, pre and post results counseling, etc)

7. Policies for research conduct/ investigator agreements:

- Investigator agrees that they will not share, sell, and distribute specimen to any third party.
- Investigator agrees that data are submitted to appropriate Intergroup data management and statistical center for matching with clinical results and statistical analysis of data.
- Investigator agrees to authorship/acknowledgement policy of Intergroup Correlative Science and Banking Committees for manuscripts, abstracts and grant submissions
- Investigator agrees that for any germline DNA study, a separate and specific informed consent must be obtained from each participant prior to extraction of DNA.

APPENDIX 10. CALGB LAB TRAK SYSTEM:
(Note; these documents describe the system during its design phase. It is now operational.)

CALGB Information Systems
Sample Submission, Tracking and Storage System
LabTrak

In the summer of 1995 the first of what promises to be many new sample banking protocols was activated by the CALGB. That protocol was CALGB 9484 and was funded through a DOD grant which provided the funds necessary to begin the development of a sample tracking system. The grant specified the development of a computerized system for tracking breast cancer samples only. However, it was soon agreed that this effort should be directed toward the tracking of all types of CALGB samples. This tracking system, dubbed "LabTrak", will provide for the collection, storage, distribution, and tracking of samples submitted by treating institutions for future research and analysis. These samples will be received, stored, processed, and shipped from specially designated labs referred to as sample banks or sample repositories. Each bank or repository will be designated as such in a banking protocol.

The purpose of this document is to provide a summary of the LabTrak system, the current status of it's development, and the currently envisioned deployment plans. The LabTrak system will be integrated into the CALGB Information System being developed at the CALGB Data Management Center. LabTrak will employ the same general requirements for design, development, and security as the rest of the CALGB Information System.

The main purpose of the LabTrak system is to keep track of CALGB samples from the time they leave the treating institution. The system will also be used to assign unique sample IDs, distribute samples for lab-based studies, ship and receive samples, request resubmission of samples, track samples for retrieval, and sending delinquent submission notifications. Also, we hope to be able to provide a labeling system to provide barcoded sample IDs that the labs can use for quick and error-free sample processing.

A. Tracking

Unique sample IDs are an integral part of the LabTrak system. Duplicate sample IDs have been a big problem when maintaining sample data within CALGB. With LabTrak, the system will assign sample IDs by querying the database to determine the next sequential sample ID. Combined with a barcode labeling and scanning system, this should remove most of the possibilities for error when dealing with sample IDs.

B. Sample IDs

Searching the sample database has many applications within CALGB. First and foremost is tracking samples and being able to pinpoint exactly where a sample has been and where it is currently located. This is very important, if for legal or ethical questions, the sample must be returned to the treating institution. The major purpose of a sample bank, or repository, is to store samples for use in

future protocols. To be able to utilize the samples stored at a bank, it is necessary to be able to search the sample database for samples meeting certain requirements and having the specific attributes required for the prospective study.

C. Distribution

Lab-based studies will need to request a random sampling of samples from one or more repositories. The LabTrak system will need to provide a method of randomizing the samples, having them processed (if necessary), and shipping them to the appropriate researcher.

D. Shipping and Receiving

Shipping and receiving samples is a very labor intensive part of a Clinical Research Associate or lab technician's job. We have attempted to design the system such that the computerized system removes much of the paperwork and logging in of samples. The system will produce shipping reports to be included with shipments. A copy of the shipment report will be sent as part of the email notification to the destination lab. Samples are grouped together into shipments which are assigned a unique shipment ID by the system. The operator can work with one or more shipments at a time. This allows the samples to be received in a lab as a group. Defaults are also used to ease this process. The condition of each sample defaults to usable, the receive date defaults to the current date, and the receiver defaults to the operator. The defaults can be applied to the currently displayed shipment or to all shipments that have been selected. This greatly reduces the work involved in logging in a shipment. A sample receipt report may also be produced which could be filed in a log book if desired.

E. Resubmission

As stated above, during sample receipt, the condition of each sample defaults to usable. Any condition other than usable is by default unusable. The selection of a condition other than usable will trigger the system to request a sample resubmission from the submitting institution. This will be done by sending email to the primary contact at that institution. The system also has a feature that will display the primary contact and the treating physician associated with the patient (remember that you must have certain privileges to see this information).

F. Retrieval

Under certain circumstances, usually involving legal issues, it may be necessary to find and return a sample to the treating institution. If the sample has been sub-sampled, it may be required that any and all parts of that sample that may have been removed from the original for analysis, also be found and returned.

G. Submission Delinquency

The system will also poll the database regularly to determine if institutions are delinquent in submitting samples for patients they have registered to various studies. An email will be sent to those institutions indicating their tardiness and detailing the patients and samples involved.

H. Email and Security Systems

Since LabTrak will be integrated into the CALGB Information System, it will employ many of the same systems such as email and security. LabTrak will use the CALGB Information Systems email system to notify the labs and treating institutions of sample shipment and receipt, as well as requests for resubmission of samples. The security system designed for the CALGB Information System will be implemented into the Labtrak system to prevent all but authorized users from accessing the patient and sample data.

I. Study Protocols

Study protocols specify the samples to be collected and submitted for that study. Sample submission information will be entered into the system as part of the schema during study definition (in the CALGB Information System) in the form of sample submission events. Sample submission events will indicate to the Clinical Research Associate at the treating institution when, what type, how many, and where to send the samples to be submitted. The Clinical Research Associate will have the ability to deviate from pre-defined submission events if necessary.

The overall system and database design has been completed. Coding and testing of the tracking, shipping and receiving, sample notes, and sample analysis portions of the system are almost complete as far as retrieval of information from the database. Updating the database with information entered still remains to be done. The data dictionary, which consists of the terms that will be used in the system to describe the attributes of samples, is undergoing review by the assigned representative from the Correlative Sciences committees. Lynn Dressler for S/T and Jim Slack for Leukemia. Currently researching methods of implementing labeling and barcodes which would initially be employed at the central labs and repositories. Integration of the barcoding software will also have to be done to allow for the importing of sample IDs to be generated as barcodes. The email and security features also need to be integrated into LabTrak and the reports formats must be designed.

Initial deployment of the LabTrak system will be as a beta test into the central labs and repositories. It has not been determined exactly which labs will be involved or how many, although the CALGB Central Pathology Lab at Roswell Park will most likely be the first beta test site. The system will not initially be distributed to treating institutions or labs other than central labs and repositories. These sites will continue to handle samples the same way they do currently. This will place an additional burden on the banks since they will have to request

sample IDs and enter all of the sample attributes into the system, but it is hoped that the other features of the system will offset this extra work. A system requirements document will be produced so that the treating institutions can see the equipment and costs associated with running the LabTrak system and the barcode labeling system. The interested institutions can then request the system through the central office. The current time frame for deployment of the beta release is targeted for the first quarter of 1997. This is also the target for bringing the central office up with the administration portion of the CALGB Information Systems as well as the Data Management Center coming up with on-line patient registration.

CALGB Sample Tracking Requirements

	Tracking System Features		
Item	**Description**	**LabTrak**	**CHTN**
1.	Sample submission events will be defined for each study such that, when selected, will provide defaults for most of the information required for a sample submission		
2.	Parent samples and sub-samples can be created with each sample or sub-sample having a unique, sequential, CALGB sample id assigned by the system.		
3.	The system will provide the ability to update or change sample attributes.		
4.	A correction history will be maintained for any changes or updates and will include who made the change and when.		
5.	Users can search for samples based on patient, study, or sample attributes.		
6.	A list of found samples will be presented after searches from which a specific sample can be selected to display all sample information.		
7.	Patient information is hidden outside the treating institution.		
8.	Create, save to the local hard disk, and restore named sample templates that contain any or all sample attributes for one or more samples.		
9.	Search for samples not shipped yet and select samples for shipment with each shipment having a unique shipment id assigned by the system.		
10.	Select shipping information relating to all samples in a shipment (destination, carrier, tracking number, ship date & time, etc.) and apply this information to all samples in the shipment.		
11.	Search for shipments based on shipping information (destination, carrier, tracking number, ship date & time, etc.) or shipment id.		
12.	Display a shipment summary with shipment id, number of samples, ship date, source and destination.		
13.	Receive shipments and apply receipt information (receiver, receive date & time, condition of sample, etc.) to all samples in a shipment.		
14.	Set the condition of individual samples in a shipment.		
15.	Select samples for reshipment to other labs (with or without sub-sample processing such as microtoming, aliquotting, etc.).		
16.	Enter and display samples notes and note dates used to document any information specific to a particular sample.		
17.	Select and display the designated analysis to be performed on a sample, the analysis date, lab, approver, and approval date.		
18.	Track a sample's location by displaying all of it's shipping records.		

	Tracking System Features		
Item	Description	LabTrak	CHTN
19.	Step through and correct errors caught when adding or updating sample data.		
20.	Maintain one additional institution or lab assigned id for each sample at each location at which it has resided.		
21.	The system will maintain the initial and current quantity of a sample.		
22.	A sample submission summary report will be included in each shipment and the email notification sent to the destination lab.		
23.	The system will provide the ability to request resubmission of samples deemed unusable.		
24.	A delinquent submission report will be produced on a regular basis and sent to the treating institutions and the responsible investigator.		
25.	The system will provide a method of invoking sample submission cutoff such that no further collection, processing, or analysis of samples is performed for a particular study.		
26.	The system will provide a method of sample labeling and bar coding which will require custom installation and configuration at each lab/repository implementing this feature.		
27.	The system will provide the means of identifying a lab as a sample repository or bank.		
28.	All tissue banks must have access to the system for recording sample tracking information.		
29.	The system will provide a method for tracking samples and sub-samples throughout their lifetime.		
30.	The system will be able to determine the location of a sample at any time after extraction.		
31.	The system will track samples for patients that are not yet registered to a study pending analysis results.		
32.	When a sample is sent to a lab, the system will send an e-mail message to notify the lab responsible contact that a sample is in transit.		
33.	Sample location will include the lab, shelf, tray, freezer, bin, box, etc. based upon the storage method and the provisions supplied at any individual lab.		
34.	Upon receipt of a sample at a lab and acknowledgment to the system, an e-mail message will be sent back to the person who sent the sample notifying them that the sample was received.		

	System Integration Issues		
Item	Description	LabTrak	CHTN
1.	Integration vs. non-integration w/ the CALGB IS		
2.	Database migration vs. disparate databases		
3.	Support for cooperative group structure		
4.	Development environment - language, GUI, database vendors		
5.	Database design methodology		
6.	Data dictionary		
7.	Communications - ODBC, C/S, remote access, security, email		
8.	Sample ids and patient confidentiality		
9.	Processing and distribution methods		
10.	Sample and shipping data fields		
11.	Study definition and tracking system integration		
12.	Collection of laboratory data		
13.	Logistics of maintaining two systems		
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APPENDIX 11. PROJECT APPROVAL LETTER TO INVESTIGATORS

Dear _____

I am pleased to inform you that your research plan has been reviewed and approved by the Steering Committee for the CALGB Linked Registry. The Protocol Editor assigned to this study is _____. He/She will be contacting you with respect to any final editing necessary to put the appendix of the protocol describing your project into final form for submission to CALGB institutions. In order for this protocol to be activated we must ask that you sign and date the both copies of this letter. Keep one for your files and return the other to the your protocol editor.

We apologize for the formality of this procedure, but we have found that written understandings of what collaboration has been agreed to is in the interest of both parties. The following text describes the nature of this collaboration :

This is a collaborative project between you and the Cancer and Leukemia Group B (CALGB). The usual ground-rules for collaborations of this type will prevail. Data from all laboratory tests performed on samples from the registry will be submitted by you to the CALGB Data Management Center. In the usual situation, transfer of this data will be via electronic means. At the Data Management Center it will be entered into the CALGB Database for analyses specified in the research plan. These analyses will be conducted by the relevant CALGB statistician. You agree that all analyses reported from your project will be based upon data contained in the CALGB Database.

Tissues and other samples are furnished to you by the Linked Registry for the purpose of the project as approved by the Steering Committee. You agree to limit your research to that described in your application unless written approval to change the scope of your investigation is obtained from the Steering Committee. You also agree that you will not furnish materials from the Linked Registry to other parties for any purpose without the written approval of the Steering Committee.

As the lead investigator, it is expected that your name will be listed as the first or last author of publications coming from this project. Other members of your research team may be granted authorship, as appropriate. CALGB personnel, usually the CALGB statistician assigned to this project, relevant members of the steering committee who are responsible for the resource used in the investigation, and others making significant intellectual contributions, will be included as authors. You will acknowledge the support of the Linked Registry Contract from the Army. You will provide the CALGB Central Office with draft copies of manuscripts 30 days prior to submission and abstracts at least 5 days prior to submission, for comment by the CALGB.

If you are not a member of CALGB but are based within a CALGB institution, you may ask that the CALGB Principal Investigator at your institution enter you on our roster. In this way you will be provided with information concerning Group activities that may bear on your project. If you are not at a CALGB institution we will enter your name in the CALGB roster as a " colleague" and ask you to choose a CALGB member as a co-investigator. If you need help in this task, please discuss this with the Chair of the Correlative Sciences Committee for Solid Tumors. The co-investigator will assist with trouble shooting problems within CALGB that may arise during the course of your investigation and will provide other assistance. Ordinarily, the co investigator will also be an author on publications.

The Steering Committee in carrying out its responsibilities for the operation of the Registry will from time to time monitor all projects using the resource. The productivity of ongoing projects and adherence to scientific and ethical standards set by the CALGB will be assessed in this

review. You agree to abide by the decisions of the Steering Committee that may come from this review.

Thank you very much and good luck with your investigation.

Sincerely yours,

O. Ross McIntyre, M.D.
Principal Investigator, Linked Registry Project

APPENDIX 12: **MILLIKAN RC, KORNBLITH AB, MCINTYRE, OR, BERRY DA, BROADWATER GJ, SANDLER DP, KARAS K, DRESSLER L, GROSS LS, COLLYAR DE, SCHILSKY RL. GENETIC TESTING IN BREAST CANCER COOPERATIVE CLINICAL TRIALS, BARRIERS AND OPPORTUNITIES. CANCER THERAPEUTICS 1:95-99, 1998**

Genetic Testing in Breast Cancer Cooperative Clinical Trials

Barriers and Opportunities

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Introduction In 1994, the cooperative cancer clinical trials group, Cancer and Leukemia Group B (CALGB), set up a registry to collect genetic and epidemiologic information from patients undergoing treatment for breast cancer. The primary goal of the registry is to investigate the predictive and prognostic value of germline mutations in cancer susceptibility genes (e.g., BRCA1, BRCA2).

Methods Patients from ongoing CALGB treatment trials are eligible for participation in data collection for the registry. The registry collects reproductive, dietary, and exposure history; germline DNA; and somatic DNA from tumor blocks. Information from laboratory assays (including genetic tests) is linked to the CALGB clinical database, which contains treatment and follow-up information.

Results Of 883 patients entered onto four CALGB treatment protocols, only 43 patients were enrolled in the registry during the first year of accrual. The majority of CALGB institutions did not approve the registry protocol because of ethical and legal concerns about the confidentiality of genetic information. Patient informed consent presented significant challenges for both oncologists and patients. We implemented procedures to address these concerns. Although enrollment increased slightly, the number of patients in the registry remains far below our expectation.

Discussion Patient confidentiality and informed consent present major obstacles for genetic studies conducted among cooperative groups. We present a series of recommendations for future projects that explore the role of genetic factors in cancer treatment. Consensus will be needed on several key issues, especially disclosure of genetic test results, informed consent, and patient confidentiality, if such projects are to go forward (*Cancer Therapeutics* 1998;1:96–100).

Key words Breast cancer, Genetic testing

It is now possible to identify carriers of germline mutations in BRCA1 (1–2), BRCA2 (3), and other cancer susceptibility genes. Estimating risk of breast and ovarian cancer for women with BRCA1 and BRCA2 mutations, particularly women who are not members of high-risk families, has been the focus of intensive research (4–6). However, the clinical significance of gene-carrier status for women already diagnosed with breast cancer is also an important area of investigation. Porter et al. (7) observed that 5-yr survival time in breast cancer patients from BRCA1-linked pedigrees was significantly greater than the survival time of breast cancer patients in general. A similar outcome for such patients with ovarian cancer was also reported by Rubin et al. (8). However, other researchers have reported that the histology and grade of breast tumors from BRCA1 and BRCA2 carriers may be associated with a worse prognosis (9–12). Because comparisons of breast cancer patients with comparable stage disease and treatment were not performed in these studies, it is impossible to determine whether gene carriers have a better or worse prognosis than patients with sporadic disease. Similarly, to determine whether germline mutations in BRCA1 or BRCA2 serve as predictive factors (indicators of patients most likely to respond to specific forms of therapy), a comparison must be made in which carriers and noncarriers receive defined forms of treatment and follow up is actively pursued. Such studies are best conducted within the context of clinical trials (13–14).

To support research aimed at identifying prognostic and predictive indicators among breast cancer patients, investigators from Cancer and Leukemia Group B (CALGB) set up a registry to collect and integrate genetic, epidemiologic, and clinical information on patients receiving therapy specified by the treatment protocols of the group. For a potential use of the registry, we were particularly interested in the effects of dose escalation for adjuvant chemotherapy and radiation among BRCA1 and BRCA2 carriers. We describe here

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the development of the project as well as obstacles encountered, and offer recommendations on how to conduct similar studies in the future.

METHODS

In 1993, CALGB obtained funding from the Department of Defense, United States Army Research and Materiel Command, for a project called Linkage of Molecular and Epidemiological Breast Cancer Investigations with Treatment Data: A Specialized Registry. Patients enrolled on four ongoing CALGB breast cancer treatment protocols were eligible for concurrent entry onto the registry: CALGB 9082 (High Dose Combination Chemotherapy for Patients with stage II or III Breast Cancer), 9342 (Taxol for Metastatic Breast Cancer), 9343 (Lumpectomy, Radiation and Tamoxifen in Patients 70 Years of Age or Older), and 9344 (Doxorubicin Dose Escalation in Patients with Node-Positive Disease). Patients were asked to contribute peripheral blood (as a source of germline DNA and plasma) as well as urine. Permission was obtained to access tumor blocks for somatic DNA and immunohistochemical assays. Baseline epidemiologic information was obtained through a telephone interview, including detailed family history, reproductive history, smoking history, alcohol consumption, and diet. A follow-up psychosocial interview was administered to a subset of patients and included scales assessing overall quality of life (physical symptoms and functioning, psychological state, body image, and family/social/sexual functioning); breast cancer-specific anxiety; and screening behaviors and attitudes toward genetic testing. All of this information was linked to the CALGB clinical database, which contains treatment and follow up information. Because our primary goal was to evaluate the prognostic and predictive value of genetic testing in patients receiving defined treatments for breast cancer, we did not interview or collect germline DNA from family members and could not enroll volunteers outside CALGB-sponsored clinical trials.

To address issues concerning informed consent and patient confidentiality, the principal investigator of the grant supporting the project (O.R.M.) convened members of the Steering Committee of the project, National Cancer Institute staff, members of cancer patient advocacy groups, representatives from the Human Genome Project, and staff from the National Institutes of Health Office for Protection from Research Risks (OPRR) to assist in developing and reviewing the patient consent form for the registry. To maximize patient confidentiality, several layers of security were used to protect the database, and the ability to link the clinical data and genetic test results was restricted to a single senior biostatistician. When obtaining informed consent we agreed that patients should have the option of participating in some or all of the activities described in the protocol (provision of germline DNA, tumor tissue for somatic DNA and immunohistochemistry, plasma, urine, and the epidemiology questionnaires). Patients who elected to provide germline DNA for BRCA1 and BRCA2 testing could choose whether or not to receive test results. After further input from breast cancer advocates, a draft of the patient consent form was developed to include the following language:

"You have indicated below whether you wish to be contacted concerning results of genetic testing. You understand that certain of the tests used by CALGB for detection of heritable cancer genes are very new, have not yet been shown to be completely reliable, and may not have been approved by the FDA for diagnostic purposes. If you wish to be informed about the outcome of genetic tests carried out on your DNA, you understand that this information is preliminary in nature, should be investigated further with additional laboratory tests, and is provided to you with these reservations."

The consent form was submitted for approval by the Institutional Review Board (IRB) at each CALGB member or affiliate institution. Participation in data collection for the registry was limited to institutions in which genetic counseling was currently available or planned for the future. To increase the number of genetic counselors with expertise in the genetics of familial cancer, the CALGB initiated a program to educate appropriate members of the group with respect to such counseling. Three full-day workshops organized by leaders in the field of cancer genetics were held to assist institutions in acquiring the skills and resources necessary to be involved in the registry.

RESULTS

In the first year of accrual (October 1, 1995 to September 30, 1996), only 43 patients were enrolled in the registry. During the same period, 883 patients were enrolled in the clinical protocols from which patients could be drawn. Thus, only 5% of eligible patients were enrolled in the registry. Only 40 of 211 CALGB institutions (19%) approved the registry protocol, and, among these institutions, only 12 enrolled patients in the registry from 1995 to 1996.

The main reasons institutions did not approve the registry protocol were legal and ethical concerns regarding patient confidentiality. Although we advised institutions on possible techniques (e.g., encryption) for protecting sensitive databases, many remained skeptical of their ability to maintain confidentiality in dealing with the information we planned to provide patients. In an attempt to further protect confidentiality of genetic test results, CALGB obtained a Certificate of Confidentiality from the Department of Health and Human Services stating that under the Public Health Service Act (42 USCA 241[d], 1988), CALGB is "authorized to protect the privacy of the individuals who are the subjects of research by withholding their names and other identifying characteristics from all persons not connected with the conduct of that research." Although not tested in court, the Certificate aims to protect institutions from involuntary disclosure of research tests to insurance providers or employers.

We also encountered several problems with informed consent. Some institutions argued strongly that we should not administer a lengthy and complex consent form for genetic testing at the same time patients faced the multiple stresses of diagnosis and randomization to

treatment for breast cancer. During pilot testing of our psychosocial questionnaire, a number of patients reported they were not aware they had given permission for genetic testing. Questioning revealed that they understood they had agreed simply to provide tissue, blood, and urine for research.

When testing for BRCA1 and BRCA2 became commercially available, the Steering Committee elected to change the status of disclosure so that information from genetic tests would no longer be provided to patients enrolled in the registry or their providers. The consent forms for the companion treatment trials were amended accordingly to include a section describing the registry, followed by a checklist where patients could indicate whether or not they consented to use of tissue, blood, or urine for research purposes. The revised consent form stated, "Neither you nor your doctor will receive the results of genetic tests." Using a single consent form for both the treatment trials and the registry simplified the process of enrollment and obtaining informed consent. Removing the need for genetic counseling allowed us to open the registry protocol to all CALGB institutions and affiliates, regardless of whether they provided such services. Finally, because results of genetic tests would not be returned to the institution for conveyance to the patient, concern about the handling of confidential information at the institutional level was no longer an issue.

After implementing the above changes, accrual to the registry increased. In the second year of accrual, 79 patients were enrolled. However, several barriers to accrual remained. Many IRBs that approved the original informed consent refused to accept a single informed consent document for treatment trials and the registry. Some institutions remained concerned that CALGB could be held liable for withholding genetic test results, even though the tests were conducted as part of a research study. Consequently, accrual to the registry remained far below our expectations.

DISCUSSION

With the discovery of familial cancer genes, there has been widespread speculation that a comprehensive understanding of the human genome will allow accurate prediction of future health or risk of disease. Whereas some have expressed concerns that this view is too optimistic (15), the current availability of testing for cancer susceptibility genes is a reality that the public and the cancer treatment community must deal with. It is imperative that we make the most of information provided by genetic tests, especially if it proves useful in guiding treatment.

To investigate whether germline BRCA1 and BRCA2 mutations affect survival and/or predict response to specific forms of treatment for breast cancer, we attempted to establish a registry of breast cancer patients on CALGB-sponsored clinical trials. A total of 112 patients were enrolled in the registry during the first 2 years of accrual, far below the number of patients needed to address our primary research questions. Because germline mutations in BRCA1 and BRCA2 mutations are rare, a registry of several thousand patients is required. For example, assuming that 5% of breast cancer patients under age 40 years are carriers of BRCA1 mutations (16), approximately 3000 such patients would be needed to detect a 10% difference in disease-free survival between carriers and non-carriers with 80% power.

A major obstacle to establishing the registry was the problem of insuring confidentiality of genetic test results within a cooperative (i.e., multi-institutional) group setting. Review of the project at our institutions occurred at a time when concern about the linkage of information about individuals from multiple government and private databases came under wide scrutiny. Originally, we arranged to provide genetic test results to patients. A number of investigators and one institution argued strongly that the field was too new and laboratory methods too uncertain to provide such feedback. This argument was countered by those who believed it unreasonable and unethical to discover that a patient carried a germline mutation and withhold this information if the patient desired to know the result. Our decision to provide test results proved problematic because the protocol could be activated only at institutions with the ability to develop and support appropriate genetic counseling procedures. Even after conducting several genetic testing workshops, we found that providing genetic counseling for cancer patients remained an insurmountable obstacle for most institutions. In addition, many institutions were not confident of their ability to maintain confidentiality of genetic test results when this information was provided to institutions for conveyance to patients.

When testing for BRCA1 and BRCA2 became commercially available, we decided not to provide genetic information to patients or their providers. We believed that patients who wished to know their BRCA1 or BRCA2 status could be referred elsewhere. However, our decision not to provide genetic test results created problems for patients and providers. Many institutions did not approve the revised registry protocol because of concern that CALGB could be held liable for withholding genetic test results from patients. The cost of commercial genetic testing may have prevented patients from pursuing testing elsewhere. Recent evidence suggests that a large percentage of the public is interested in hereditary cancer risk notification and testing (17).

We encountered several problems with informed consent. To participate in data collection for the registry, breast cancer patients were asked to consent to the use of germline DNA at the same time they faced the stress of diagnosis and randomization to treatment. We sought to enroll patients in the registry at the time of initiation of cancer treatment in order to obtain pre-treatment DNA specimens so as not to confound assay results by exposure to cytotoxic chemotherapy. The inability of a number of patients who signed consents for our genetic studies to recollect a few weeks later that they had done so is a sobering reality. If it could be established that germline DNA collected during or after chemotherapy and/or radiation represented a resource equivalent to that of DNA collected before treatment, informed consent could be obtained at a time less stressful to the patient.

Other aspects of informed consent must be addressed for genetic studies involving cancer patients. Recent policy statements agree that informed consent is required for all genetic research in which results can be linked to individuals (18–20). Based on our experience, if patients are to be truly informed of the nature of the research in which they are participating, some genetic counseling is needed during the informed consent process. Currently, only half of NCI-sponsored cancer centers offer genetic counseling for cancer patients (21). It has been argued that patients should be fully informed of the use of DNA specimens, regardless of whether test results are to be provided (22). However, disclosure of all potential genetic testing is impossible for loci which have yet to be discovered. More important, listing of laboratory tests to be performed on consent forms may require patients to answer affirmatively to employers or insurers who inquire whether they have undergone genetic testing, even though they will not learn the results of the tests (23). Attention has been given to establishing guidelines for processing and storage of biologic samples (24), but the "ownership" (or control for purposes of research) of patient blood and tumor tissue remains a contentious issue, especially in cooperative groups (25). Finally, genetic studies carry strong negative connotations for members of some racial and ethnic groups (26) and could threaten a recent trend of greater participation of minority groups in cancer treatment trials (27).

Until more is known about the clinical implications of BRCA1 or BRCA2 status, there is little likelihood that there will be any benefit to patients who participate in data collection for cooperative group registries such as ours. This issue has likely exacerbated the problems of patient confidentiality and informed consent. We are committed to developing an appropriate method for conveying genetic test results to patients and their providers should insights be gained from our research that could benefit participants in the future. Delivery of such information depends on devising accurate laboratory screening methods to avoid misclassification of gene status (28), discovering strategies for minimizing the adverse psychological effects of genetic testing (29–30), and developing uniform standards for the scope of disclosure and future use of genetic samples (31). New strategies for protecting patient confidentiality in research, such as the designation of "tissue trustees," must be explored (32). A recent report issued by the National Institutes of Health Task Force on Genetic Testing (33) demonstrates that considerable progress is being made on these issues. We believe that genetic testing may some day help identify patients most likely to respond to treatment, sparing patients for whom the treatment will not work. Based on recent evidence that BRCA1 and BRCA2 may play a role in DNA repair (34–35), it has become increasingly important to evaluate the relationship between gene carrier status and response to ionizing radiation treatment and specific forms of adjuvant chemotherapy (36–38). For this reason, despite many obstacles, we believe studies of this type must go forward.

RECOMMENDATIONS

Following is our series of recommendations for future studies that involve genetic testing in cooperative groups. These suggestions may be useful as projects such as Cancer Genetics Networks (39) are established. Such studies require close collaboration between physicians, molecular biologists, psychologists, public health professionals, and most important, patients and patient advocacy groups (40–41).

1. Consensus building and agreement on goals is necessary at the design stage of cooperative group registries. To address anxiety among clinicians, institutions, and patients surrounding genetic testing, methods for addressing patient and institutional confidentiality must be agreed upon before such projects are implemented.
2. Protection from discrimination is essential for patients who participate in genetic research. Legislation is needed to prohibit insurers and employers from inquiring whether a patient has undergone genetic testing in a research setting.
3. A Certificate of Confidentiality issued by the Public Health Service is an important safeguard for genetic research. A long lead time for obtaining the certificate should be anticipated when the project is conducted among multiple institutions (42).
4. An agreement should be reached among federal and institutional bodies responsible for the protection of human subjects regarding appropriate methods for linking patient DNA samples with patient identifiers.
5. A consensus statement must be developed by patient advocacy groups, independent investigators, legal counsel, and administrators regarding standardized language for informed consent in genetic studies. In particular, the nature of genetic research and methods for safeguarding genetic information must be explained carefully to patients.
6. The number of genetic counselors with special expertise in familial cancer genes must be increased. Genetic counselors should participate in the process of informed consent for genetic studies, regardless of whether results are to be provided to patients.
7. Standards for disclosure or nondisclosure of genetic information to patients and their families must be developed. There is widespread disagreement among experts concerning the ethics of providing results of genetic tests to participants in research studies. In contrast to laboratory tests that are licensed for diagnostic purposes, genetic screening methods are often preliminary in nature and will, at times, lead to erroneous conclusions. If such information is to be disclosed to participants, appropriate counseling must be provided.

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